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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

Appellants: Bartley et al.

Serial No.: 08/347,780

Group Art Unit No.: 1812

Filed: November 30, 1994

Examiner: Spector, L.

For: COMPOSITIONS AND METHODS FOR STIMULATING
MEGAKARYOCYTE GROWTH AND DIFFERENTIATION

Docket No.: A-290C

BRIEF FOR BARTLEY ET AL.

RECEIVED

MAR - 2 1998

Assistant Commissioner for Patents
Washington, D.C. 20231

MATRIX CUSTOMER
SERVICE CENTER

Sir:

Appellants appeal from the final rejection dated February 14, 1997 of claims 78-89 of this application.

Real Party In Interest

Amgen Inc.

Related Appeals and Interferences

None.

Status of Claims

Claims 1-77 are cancelled in this application. Claims 78-89 are rejected in this application and are also appealed herein.

Status of Amendments

In the Advisory Action dated October 10, 1997, the Examiner has indicated that the amendments proposed by Appellants in their response to the final rejection filed August 19, 1997 will be entered. Claims 78-89, as provided in Appendix A hereto, contain all of the proposed amendments.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231, on the date appearing below.

February 17, 1998

Date

Julia A. Killion

Signature

Summary of Invention

The present invention relates to isolated polynucleotides (PNs) encoding certain biologically active *fragments* of the amino acid sequence set forth in SEQ ID NO. 25, attached hereto as Appendix B. (See page 17, lines 33-35; page 33, lines 28-35; page 36, lines 11-31; and page 37, lines 1-8 of the specification¹.) SEQ ID NO. 25 shows an amino acid sequence that begins at amino acid -21, continues through to amino acid 1 (the beginning of the mature protein), and then continues until the last amino acid of the mature protein, amino acid 332. (See FIG. 11 of the specification.) This full-length mature protein is known as thrombopoietin (TPO) and has the biological activity of stimulating platelet production *in vivo* through promoting growth and differentiation of megakaryocytes (platelet precursor cells). (See page 36, lines 32-36 of the specification.)

The PNs of the claimed invention encode certain fragments of TPO (SEQ ID NO: 25) that commence either at amino acid -21 (Claim 78) or at amino acid 1 (Claim 79) and terminate at an amino acid selected from amino acids 151 through 244 of SEQ ID NO. 25. (See page 35, lines 11-16 of the specification.) Therefore, for example, the present claims embrace PNs encoding the following representative polypeptides:

Claim 78

-21	..	1	..	151
Met	..	Ser	..	Cys
-21	..	1	..	152
Met	..	Ser	..	Val
.				
.				
-21	..	1	..	244
Met	..	Ser	..	Ser

¹ In a response filed November 26, 1996, Appellants herein amended the current specification to reflect the numbering system wherein the first amino acid of the mature MGDF polypeptides is assigned the number "1." Therefore, the MGDF species of page 37, lines 1-8 are as follows:

MGDF-4	amino acids	1-151	FIG. 11
MGDF-5	amino acids	1-156	FIG. 11
MGDF-6	amino acids	1-170	FIG. 11
MGDF-7	amino acids	1-177	FIG. 11
MGDF-8	amino acids	1-244	FIG. 11
MGDF-11	amino acids	1-163	FIG. 11

Note that the claimed range 1-151 through 1-244 is supported by the above examples.

Claim 79

1	..	151
Ser	..	Cys
1	..	152
Ser	..	Val
.	.	.
1	..	244
Ser	..	Ser

Notably, although the claimed PNs encode polypeptides that are significantly truncated relative to full-length TPO, they retain substantially the biological activity of full-length TPO. This unexpected property is reflected in the claims' requirement that all of the encoded polypeptides have an activity of specifically promoting megakaryocyte growth or differentiation. A representative example of the instant claimed PNs is DNA encoding amino acids 1-163 of SEQ ID NO: 25, designated MGDF-11, which is shown at Table 10, page 95 of the specification, to stimulate production of megakaryocytes in mice. (See also page 95, lines 9-14 of the specification.)

Dependent Claim 80 is directed to PNs having codons immediately 5' to the PNs of Claim 79 which additionally encode the peptide Met-Lys. (See page 19, lines 1-12; page 97, lines 5-13 of the specification.) Thus, the PNs of Claim 80 are those that encode the polypeptides starting at amino acid position 1 (Ser) and terminating at an amino acid selected from 151 through 244 of SEQ ID NO. 25, and further having a Met-Lys dipeptide attached to the N-terminus of the polypeptide, for example:

-2	-1	1	..	151
Met	Lys	Ser	..	Cys
-2	-1	1	..	152
Met	Lys	Ser	..	Val
.
-2	-1	1	..	244
Met	Lys	Ser	..	Ser

Dependent Claim 81 is directed to PNs of the previous claims that are DNA sequences, while dependent Claims 82-84 are directed to particular DNA sequences. (See page 17, lines 35-36; page 18, lines 1-5 of the specification.)

Dependent Claim 85 is directed to a DNA vector comprising a DNA of Claim 81. (See page 18, lines 10-12 of the specification.)

Dependent Claim 86 is directed to a DNA vector wherein a DNA of claim 81 is operatively linked to an expression control DNA sequence. (See page 18, lines 12-16 of the specification.)

Claims 87-88 are directed to host cells that are transformed or transfected with a DNA of Claim 81 (Claim 87) and that express this DNA (Claim 88). (See page 18, lines 12-20 of the specification.)

Finally, Claim 89 is directed to methods for producing a polypeptide which involves growing a host cell according to Claim 88 and isolating the polypeptide produced. (See page 18, lines 21-36 of the specification.)

Thus, the present claimed invention is directed to PNs that encode a readily definable collection of polypeptides and related aspects (i.e., vectors, cells, and methods).

Issue

The single rejection on appeal is a provisional non-statutory obviousness-type double patenting rejection of all pending Claims 78-89 over all allowed Claims 36-44 (now Claims 37, 38, and 40-46) of co-pending application Serial No. 08/252,628 ("the '628 application").² The allowed claims of the '628 application, attached hereto as Appendix C, generally relate to PNs that encode a *full-length* polypeptide consisting of amino acids 1 through 332 of the sequence of SEQ ID NO. 25. All of the dependent claims of the '628 application are related to PNs encoding this full-length polypeptide sequence, which is specified in independent Claim 45.

² In a response dated November 4, 1996 filed in the '628 application, Appellants canceled Claims 36 and 39 and added new Claims 45 and 46 therein. These new claims embrace essentially the same subject matter as prior Claims 36 and 39 of that application. Accordingly, it is believed that the Examiner intended the current double patenting rejection of Claims 78-89 in this application (the '780 application) to be over Claims 37, 38, and 40-46 of the '628 application.

Thus, the issue on appeal is:

1. Does an allowed claim to polynucleotides encoding full-length TPO protein provide a proper basis for an obviousness-type double patenting rejection of claims addressing polynucleotide fragments possessing an unexpected property?

Grouping of Claims

Appellants submit that the present Claims 78-89 do not stand and fall together. Claims 80, 82 and 84, which are directed to PNs encoding polypeptides with an amino-terminal Met-Lys dipeptide, are separately patentable because none of the '628 patent claims disclose such a Met-Lys dipeptide. Claim 85 (a DNA vector), Claim 86 (requiring that the DNA encoding the polypeptide fragment be *operably linked to an expression control DNA sequence*), Claims 87-88 (host cells) and Claim 89 (method of making a polypeptide) are separately patentable because they specifically relate to the unexpected property of the PNs of the invention, *i.e.*, encoding a biologically active polypeptide.

Arguments

Appellants submit that the provisional obviousness-type double patenting rejection of claims relating to PNs encoding certain biologically active fragments of TPO over claims relating to PNs encoding *full-length* TPO should be reversed because, for the reasons explained below, it lacks both a legal and a scientific factual basis.

"An obviousness-type double patenting rejection prevents applicants from extending their patent term beyond statutory limits where an application claims merely an obvious variant of the claims in a prior patent." *In re Emert*, 44 USPQ2d 1149, 1152 (Fed. Cir. 1997). In making this determination, only the *claims* of the prior patent (or allowed application claims), not the disclosure contained in the specification, may be considered. See *In re Kaplan*, 229 USPQ 678, 682 (Fed. Cir. 1986). The analysis under the doctrine of obviousness-type double patenting, like the analysis under 35 U.S.C. § 103, requires the Examiner to establish a *prima facie* case of obviousness. *In re Longi*, 759 F.2d 887, 895, 225 USPQ 645, 651 (Fed. Cir. 1985).

The Examiner's position in the final rejection of February 14, 1997 was that:

In the instant case the Examiner maintains the position that
the *truncated DNAs are obvious over the full-length*, as it

would have been obvious to the person of ordinary skill in the art, having the full length, to use subsets of such for example as hybridization probes, etc. Thus, the claimed compositions themselves are obvious. With regard to applicants argument that it would not have been predictable that such truncations would retain the ability to encode a protein with biological activity, it is noted that such a property is merely an inherent property of the obvious nucleic acids. It has long been established that the mere recitation of a newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art (*In re Swinehart and Sfiligoj*, 169 USPQ 226)." [Emphasis added.]

In the Advisory Action, the Examiner reiterated that "truncation is obvious, applicants are claiming [a] broad range of species." Of course, the issue of whether a range of species is broad or narrow is a relative one. Considering the broadest Claims 78 and 79 under appeal, it is clear that the PNs claimed therein have some very specific requirements in terms of the encoded polypeptides. As explained above, the encoded polypeptides must begin with either amino acid -21 of SEQ ID NO. 25 or amino acid 1 of SEQ ID NO. 25 and terminate with an amino acid selected from residues 151 through 244 of SEQ ID NO. 25. This claimed subset of PNs is substantially smaller than the range of all possible fragments of the full-length PNs, which in the broadest sense could involve fragments consisting of even a single base. In fact, the claimed subset is substantially smaller than the set of all truncated PNs that encode biologically active protein, because PNs encoding polypeptides terminating at amino acids 245 through 332 (which, *a fortiori*, would also be biologically active) are excluded from the claims. Appellants therefore are claiming a relatively narrow range of species that moreover possesses an unexpected property, i.e., encoding a biologically active polypeptide.³

³ In this case, one of ordinary skill could not have predicted that such extensive truncation, i.e., elimination of nucleotides corresponding to from 88 to 181 amino acids out of 332 (27% to 55% of the full-length protein), would result in a PN encoding a protein that retained a biological activity of the same type as the native molecule. Appellants submit that one skilled in the art would have had either no expectation as to the activity of the truncated proteins, or more likely would have expected such truncation to abolish activity. Again, the instant claims require that the polypeptides encoded by the claimed PNs have the activity of specifically promoting megakaryocyte growth or differentiation.

In support of their position, Appellants call attention to *Genentech Inc. v. The Wellcome Foundation Ltd.*, 31 USPQ2d 1161 (Fed. Cir. 1994) (attached hereto as Appendix E), in which the Federal Circuit (C.A.F.C.) held that a truncated variant of tPA did not infringe a claim in a U.S. patent to "human" tPA. The variant, referred to as FE1X, was missing 81 amino acids (15% of the full-length

Even assuming that the Examiner is correct in asserting that the group of truncated PNs that are hypothetically useful as "probes, etc." is obvious in light of full-length PN, this group does not fully overlap the claimed group of PNs because only fragments of a *native, naturally occurring PN* will be useful as probes. In contrast, Claims 78 and 79 are not limited to the naturally occurring sequence but rather are directed to *any* PNs that encode the specified polypeptides. Thus, numerous (native sequence) PNs useful as probes are *not* embraced by the claims, and, more importantly, numerous PNs embraced by the claims are *not* potentially useful as probes. The claimed PNs that are not useful as probes are not rendered obvious according to the Examiner's rationale that truncated native sequence PNs might be useful as probes.

Even those of the claimed PNs that *are* potentially useful as probes are not obvious as a matter of law because they are shown by the present specification to possess an unexpected property that renders them patentably distinct from the full-length PNs. In this regard, Appellants call attention to *In re Papesch*, 137 USPQ 43 (CCPA 1963) (filed herewith as Appendix D), which stands for the proposition that if structurally obvious compounds have unexpected properties, i.e., properties not disclosed or suggested by the prior art, then it is not, as a matter of law, obvious to produce such compounds. This proposition has been reiterated in *In re Dillon*, 16 USPQ2d 1897 (Fed. Cir. 1990), *cert. denied*, 500 U.S. 904 (1991). In analyzing the previous case law dealing with this issue, the Court in *Papesch* stated that:

Where what we may call the apparent obviousness of the compound (including its properties) was overcome by evidence of unexpected advantageous properties the claim to it was held patentable; but where no such properties were shown to exist it remained an obvious compound with

protein) as compared with natural human tPA and had two additional single amino acid changes. The Court stated that these changes led to a "dramatically different" structure [*Genentech*, page 1171]. On the basis of the "profound differences in structure and properties" (*Ibid.*, page 1172), the Court concluded that FE1X did not infringe the patent. Judge Lourie in his concurring opinion regarded the 15% change as "substantial." The Court therefore essentially concluded in *Genentech* that the invention of a full-length human tPA was a different invention from a truncated protein missing 15% of the full-length protein. In this case, it would seem to be even more unpredictable that PNs encoding a truncated protein that is missing 27% to 55% of the full-length TPO molecule would encode a biologically active polypeptide.

obvious properties. [Papesch, page 49; emphasis added.]

In this case, the apparent obviousness of the truncated PNs that are useful as probes is overcome by the evidence of unexpected advantageous properties, *i.e.*, encoding polypeptide fragments with biological activity.

Additional support for Appellant's position is found in *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993), attached hereto as Appendix F . In *Bell*, although the Patent Office advocated the position that a human cDNA was rendered obvious by the known amino acid sequence of the protein, the Court stated that:

It may be true that, knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. * * * *

Therefore, given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious. [*Bell*, page 1531.]

Similarly, in this case, given the infinite number of possible truncations of the PNs encoding full-length TPO, and the failure of the '628 application claims to suggest the particular limitations of Claims 78 and 79 (*i.e.*, PNs encoding polypeptides commencing either at residue -21 or at residue 1 and terminating at any one of residues 151 through 244) and the unexpected biological activity of the encoded polypeptides, the presently claimed PN sequences would not have been obvious.

The Examiner's rejection therefore lacks a scientific factual basis because not all of the claimed PNs possess the allegedly obvious property of being useful as hybridization probes, and furthermore lacks a legal basis because a discovery of unexpected properties for even purportedly structurally obvious compounds (*e.g.*, significantly truncated fragments of a generic, full-length sequence) renders these compounds patentable. The Examiner's suggestion that the unexpected properties are "inherent" in the PN fragments claimed is without legal significance. That which may be inherent is necessarily not known, and cannot provide a basis for obviousness of the

claimed subject matter. *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966).

Appendix G depicts in Venn diagram format the various groups of full-length and truncated PNs of the two sets of claims. It is apparent that the claimed invention is not commensurate in scope with either all possible truncations, or with the truncated species useful as probes.

Claims 80, 82, and 84 relate to PNs encoding polypeptides beginning with Met-Lys. It is not seen how this additional limitation is rendered obvious by any of the pending claims in the '628 application. The Office is not permitted to rely on the disclosure of the '628 application in making the double patenting rejection herein, but rather only the claims. None of the claims of the '628 application include a Met-Lys dipeptide and there is no reason apparent from these claims why the Met-Lys codons would be obvious. Thus, Claim 80 is clearly unobvious from the prior *claimed* invention. Moreover, it is noted that SEQ ID NO. 28 referred to in Claim 82 and SEQ ID NO. 29 referred to in Claim 84 both require Met-Lys at the N-terminal of the polypeptide, and therefore, such additional claims are clearly unobvious over the prior pending claims as well.

With regard to Claims 85-89, these claims are directed to a DNA vector (Claim 85), a DNA vector in which the DNA encoding the polypeptide is operably linked to an expression control DNA sequence (Claim 86), a host cell (Claims 87 and 88), or a method for producing a polypeptide (Claim 89). The Examiner stated that the reason the PN truncations of TPO are obvious from the full-length PNs encoding TPO was that the truncated PNs could be used as "probes, etc." Even granting the Examiner's position that potential utility of DNA fragments as probes renders some truncated native sequence PNs obvious, it does not follow that it would be obvious to incorporate such probes in a vector, particularly in operable linkage to an expression control sequence, or in host cells, or to employ them in a method for producing a polypeptide. The inventions claimed in Claims 85-89 are specifically based on Appellants' teaching that the truncated PNs of the present claims encode active proteins. Otherwise, why would one include such PNs in a vector, put such vector in a host cell, and use such host cell to produce a polypeptide? Because this is information that cannot be derived from any claim of the '628 application, it is submitted that Claims 85-89 are each patentably distinct from the claims in the '628 application.

In light of the above arguments and cited authorities, it is submitted that the present claims are patentably distinct from the claims of the '628 application. Accordingly, the Board is respectfully requested to reverse the Examiner's final rejection of non-statutory double patenting and to find them in condition for allowance.

Appendix

Appendix A: Pending claims on appeal in U.S. Serial No. 08/347,780.

Appendix B: SEQ ID NO. 25.

Appendix C: Pending claims of U.S. Serial No. 08/252,628.

Appendix D: *In re Papesch*, 137 USPQ 43 (CCPA 1963).

Appendix E: *Genentech Inc. v. The Wellcome Foundation Ltd.*, 31 USPQ2d 1161 (Fed. Cir. 1994)

Appendix F: *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993)

Appendix G: Venn Diagram

Respectfully submitted,



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APPENDIX A

A-290C (as amended 10/96)
Serial No.: 08/347,780

Truncated DNA Claims

78. An isolated polynucleotide encoding a polypeptide consisting of the amino acids X - Y - Z of SEQ ID NO: 25, wherein X is -21, Y is -20 through 150, and Z is selected from the group consisting of amino acids 151 through 244, wherein said polypeptide has an activity of specifically promoting megakaryocyte growth or differentiation.

79. An isolated polynucleotide encoding a polypeptide consisting of the amino acids X - Y - Z of SEQ ID NO: 25, wherein X is 1, Y is 2 through 150, and Z is selected from the group consisting of amino acids 151 through 244, wherein said polypeptide has an activity of specifically promoting megakaryocyte growth or differentiation.

80. An isolated polynucleotide according to Claim 79, further encoding the dipeptide Met-Lys immediately 5' to the codon for X.

81. An isolated polynucleotide according to any of Claims 78, 79, or 80 which is a DNA sequence.

82. A DNA sequence according to Claim 81, which has the sequence set forth in SEQ ID NO: 28.

83. A DNA sequence according to Claim 81, which is a cDNA sequence.

84. A cDNA according to Claim 83, which has the corresponding nucleotide sequence of SEQ ID NO: 29.

85. A DNA vector comprising a DNA sequence according to Claim 81.

86. The DNA vector of Claim 85, wherein said DNA sequence is operatively linked to an expression control DNA sequence.

87. A host cell stably transformed or transfected with a DNA according to Claim 81.

88. A host cell according to Claim 87, which expresses said DNA sequence.

89. A method for producing a polypeptide, said method comprising growing a host cell according to Claim 88 in a suitable nutrient medium and isolating said polypeptide from said cell or said nutrient medium.

APPENDIX B

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 354 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Glu Leu Thr Glu Leu Leu Val Val Met Leu Leu Leu Thr Ala
-21 -20 -15 -10

Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys Asp Leu Arg Val
-5 1 5 10

Leu Ser Lys Leu Leu Arg Asp Ser His Val Leu His Ser Arg Leu Ser
15 20 25

Gln Cys Pro Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala
30 35 40

Val Asp Phe Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys
45 50 55

Ala Gln Asp Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met
60 65 70 75

Ala Ala Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
80 85 90

Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln Ser Leu
95 100 105

Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp
110 115 120

Pro Asn Ala Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val
125 130 135

Arg Phe Leu Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg Arg Ala
140 145 150 155

Pro Pro Thr Thr Ala Val Pro Ser Arg Thr Ser Leu Val Leu Thr Leu
160 165 170

Asn Glu Leu Pro Asn Arg Thr Ser Gly Leu Leu Glu Thr Asn Phe Thr
175 180 185

Ala Ser Ala Arg Thr Thr Gly Ser Gly Leu Leu Lys Trp Gln Gln Gly
190 195 200

Phe Arg Ala Lys Ile Pro Gly Leu Leu Asn Gln Thr Ser Arg Ser Leu
205 210 215

Asp Gln Ile Pro Gly Tyr Leu Asn Arg Ile His Glu Leu Leu Asn Gly
220 225 230 235

Thr Arg Gly Leu Phe Pro Gly Pro Ser Arg Arg Thr Leu Gly Ala Pro
240 245 250

Asp Ile Ser Ser Gly Thr Ser Asp Thr Gly Ser Leu Pro Pro Asn Leu
255 260 265

Gln Pro Gly Tyr Ser Pro Ser Pro Thr His Pro Pro Thr Gly Gln Tyr
270 275 280

Thr Leu Phe Pro Leu Pro Pro Thr Leu Pro Thr Pro Val Val Gln Leu
285 290 295

His Pro Leu Leu Pro Asp Pro Ser Ala Pro Thr Pro Thr Pro Thr Ser
300 305 310 315

Pro Leu Leu Asn Thr Ser Tyr Thr His Ser Gln Asn Leu Ser Gln Glu
320 325 330

Gly *

APPENDIX C

A-290A (as amended 11/96)
U.S. Serial No. 08/252,628

Full-Length DNA Claims

37. An isolated polynucleotide according to Claim 45 which is a DNA sequence.
38. A DNA sequence according to Claim 37, which is a cDNA sequence.
40. A DNA vector of comprising a DNA sequence according to Claim 37.
41. The vector of Claim 40 wherein said DNA sequence is operatively linked to an expression control DNA sequence.
42. A host cell stably transformed or transfected with a DNA sequence according to Claim 37.
43. A host cell according to Claim 42, which expresses said DNA sequence.
44. A method for producing a polypeptide, said method comprising growing a host cell according to Claim 43 in a suitable nutrient medium and isolating said polypeptide from said cell or said nutrient medium.
45. An isolated polynucleotide encoding a polypeptide consisting of the amino acid sequence 1-332 of SEQ ID NO: 25.
46. A cDNA according to Claim 38, consisting of the nucleotide sequence 99-1094 of SEQ ID NO: 24.

50 CCPA 1084

Court of Customs and Patent Appeals

In re PAPESCH

Appl. No. 6882 Decided Mar. 20, 1963

PATENTS

1. Patentability—Invention—Law or fact question (§ 51.507)

Issue of law is involved where claims are rejected only on ground that they are unpatentable over a single reference which discloses what is conceded to be a lower homolog of claimed compounds and proof has been given showing that representative member of group of claimed compounds possesses advantageous property shown not to be possessed by prior art compound.

2. Claims—Process (§ 20.80)

Patentability—New use or function—Process (§ 51.561)

Only way in which a "use" can be claimed is as a process.

3. Patentability—Composition of matter (§ 51.30)

Words and phrases (§ 70.)

Court agrees that such similarity in structure as exists in instant case probably indicates similarity in some undislosed properties, but does not give too much legal significance to bare term "homolog," even where there is an admission of homology; term is often used loosely.

4. Patentability—Invention—In general (§ 51.501)

Court accepts in principle the statement that 35 U.S.C. 103 requirement of unobviousness is no different in chemical cases than with respect to other categories of patentable inventions.

5. Patentability—Invention—Law or fact question (§ 51.507)

Problem of "obviousness" under 35 U.S.C. 103 in determining patentability of new and useful chemical compounds is not a problem in chemistry or pharmacology or in any other related field of science, but is a problem of patent law.

6. Patentability—Invention—In general (§ 51.501)

35 U.S.C. 103 is statutory version of what was, prior to January 1, 1953, the judge-made requirement of "invention."

7. Patentability—Composition of matter (§ 51.30)

In re Hass, 60 USPQ 544, 548, 552, and *In re Henze*, 85 USPQ 261, suggest, by way of dicta, that proof of existence of unobvious or unexpected beneficial

properties in a new compound, which would otherwise appear to be obvious (along with its properties), is indicative of presence of invention and hence of patentability; what this comes down to is that, if that which appears, at first blush, to be obvious though new is shown by evidence not to be obvious, then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall.

8. Patentability—Invention—In general (§ 51.501)

In most respects, "invention" is pre-revision equivalent of "unobviousness" requirement of 35 U.S.C. 103.

9. Patentability—Composition of matter (§ 51.30)

In re Henze, 85 USPQ 261, did not use "those skilled in the chemical art" and "chemists" in such a narrow sense as to exclude biologists, pharmacologists, medical clinicians, or any other competent trained personnel who carry on investigative work in general field of drugs.

10. Patentability—Composition of matter (§ 51.30)

Cited cases show that, both before and after enactment of 35 U.S.C. 103, courts determined unobviousness and patentability of new chemical compounds by taking into consideration their biological or pharmacological properties; patentability was not determined on basis of obviousness of structure alone.

11. Patentability—Composition of matter (§ 51.30)

It is error of law to fail to take into consideration the biological or pharmaceutical property of claimed compounds on ground that to chemists the structure of compounds would be so obvious as to be beyond doubt, and that a showing of such properties is to be used only to resolve doubt.

12. Patentability—Composition of matter (§ 51.30)

From standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing; graphic formulae, chemical nomenclature, systems of classification and study such as concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared; but a formula is not a compound and, while it may serve in a claim to identify what is being patented, thing that is patented is not formula but compound identified by it; patentability of the thing does not depend on similarity of its formula to that of another compound but of similarity

of the former compound to the latter; there is no basis in law for ignoring any property in making such a comparison; an assumed similarity based on comparison of formulae must give way to evidence that assumption is erroneous.

13. Claims—Process (§ 20.80)

Patentability—Composition of matter (§ 51.30)

Chemical compound need not be claimed as a process utilizing newly discovered property of compound, but product claims may be allowed.

14. Patentability—Composition of matter (§ 51.30)

In determining obviousness of chemical compound, there may be other factors to consider than a difference of a single advantageous property; thus, it is important if prior art disclosure is not merely of a structurally similar compound but also, at least to a degree, of the same desired property relied on for patentability in new compound; such other factor must be considered because it bears on obviousness of compound, which is, realistically and legally, a composite of both structure and properties.

Particular patents—Trialkyl Compounds

Papesch, 2,4,6,-Trialkylpyrazolo [4,3-d]-4,5,6,7-Tetrahydropyrimidine - 5,7-Diones, claims 1 and 3 of application allowed.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Viktor Papesch, Serial No. 836,870, filed Aug. 31, 1959; Patent Office Division 6. From decision rejecting claims 1 to 3, applicant appeals. Reversed.

HELMUTH A. WEGNER, Chicago, Ill., for appellant.

CLARENCE W. MOORE (RAYMOND E. MARTIN of counsel) for Commissioner of Patents.

Before WORLEY, Chief Judge, and RICH, MARTIN, SMITH, and ALMOND, Associate Judges.

RICH, Judge.

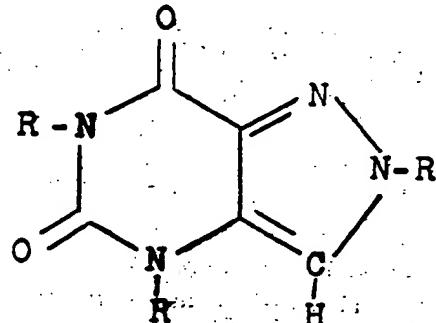
This appeal is from the decision of the Patent Office Board of Appeals affirming the rejection of claims 1-3, the only claims presented in appellant's application Ser. No. 836,870, filed August 31, 1959, for "2,4,6-Trialkylpyrazolo [4,3-d]-4,5,6,7-Tetrahydropyrimidine - 5,7-Diones."

The specification, which is brief and occupies less than three pages of the printed record, states:

The trialkyl compounds of this invention have been found to possess unexpectedly potent anti-inflammatory activity in contrast to the related trimethyl compound. The instant compounds are also diuretic agents.

Claims 1 reads:

A compound of the structural formula



wherein R is a lower alkyl radical containing more than one and less than five carbon atoms.

Claim 2 is specific to a compound within claim 1 wherein each R is an ethyl radical (which has, inter alia, 2 carbon atoms) and claim 3 is specific to the n-butyl compound wherein the alkyl radicals each contain 4 carbon atoms.³ There are no other claims and the legal issue is such that it is unnecessary to distinguish between the claims.

Application Prosecution

The prosecution of this application was truly compact. On the first action the examiner rejected the claims on a single reference:

Robins et al., J. Am. Chem. Soc., Vol. 78, pp. 2418-2422 (1956).

The action is so brief and to the point that we quote it in full:

Claims 1-3 are rejected as being unpatentable over Robins et al. Note Compound XVI. The ethyl and n-butyl side chains depicted in applicant's claims 2 and 3 are obvious homologs of the methyl groups shown in identical positions in the reference compound and the method of preparation is substantially the same. (In re Henze, 636 O.G. 698, 85 USPQ 261). [Emphasis added].

Compound XVI of the Robins et al. article is described by its structural formula which would be identical with that of appellant's claim 1, supra, if all of the three R's therein were methyl, -CH₃, producing a trimethyl compound. There is textual reference to this and two other formulae, reading as follows:

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Methylation of 5,7 - dihydroxypyrazolo [4,3 - d] - pyrimidine with dimethyl sulfate in the presence of sodium hydroxide gave a compound $C_8H_{10}O_4N$, isomeric with caffeine, presumably 1,4,6 - trimethylpyrazolo [4,3 - d] pyrimidine - 5,7 - dione (XV), although the possibility of the isomeric structure XVI for this compound has not been entirely eliminated. It is interesting to note that under the conditions of the experiment only one isomer was isolated. [Emphasis ours.]

By reason of this speculation on the part of Robins et al. as to whether they really produced XV or XVI, appellant points out that what the Patent Office relies on as prior art to show obviousness of the claimed compounds is the formula considered least likely by the authors. However, we give no weight to the speculative nature of the prior art compound because we do not believe that, in final analysis, appellant does so. His brief states:

The Robin et al. reference discloses, at best, that the lower homolog of the claimed compounds may possibly exist, as a less likely alternative, and, if it does, how it is formed.

The case is really argued, however, on the assumption that a lower homolog of the claimed compounds is in the prior art and we shall proceed on that assumption. In other words, comparing the specific compound of claim 2 with the prior art, the compounds differ only in that where appellant has three ethyl groups the prior art has three methyl groups, a total difference of three $-CH_2-$ groups. Whether this meets the usual definitions of "homology" (according to two additional references to chemical texts made of record by the Patent Office) we do not stop to consider inasmuch as appellant has not argued the point.¹ Indeed, we do not see why the Robins et al. compound XVI is not "the related trimethyl compound" referred to in the specification, quoted above.

The claims having been rejected on Robins et al., appellant responded by filing the affidavit of Dr. Francis J. Saunders (Ph.D. 1937), physiologist and

a member, since 1938, of the Biology Division of G. D. Searle & Co., owner of the application at bar. Dr. Saunders has been in charge of Searle's endocrinological and related physiological research. The affidavit reports comparative tests of the Robins et al. trimethyl compound and appellant's triethyl compound which show that the latter is an active anti-inflammatory agent while the prior art compound is completely inactive in that respect. We need not examine the tests in detail because the Patent Office has accepted the factual conclusions of the affiant based on them.

[1] We have before us, therefore, a single clean-cut issue of law. The claims are rejected only on the ground that they are unpatentable over a single reference which discloses what is conceded to be a lower homolog of the claimed compounds (whether or not all chemists would so consider it) and proof has been given showing that the compound of claim 2, "a representative member of" the group of compounds claimed, possesses an advantageous pharmacological property shown not to be possessed by the prior art compound. In filing the affidavit, appellant stated in his response to the office action that the compounds of his claims 1 and 3 included more distantly related compounds than the triethyl compound tested and submitted that the showing of unpredictable and "completely dissimilar biological properties" established the patentability of the compounds he claimed.

The Examiner's Views

The reply to this first response was a final rejection stating, in pertinent part:

The claimed compounds are obvious under 35 U.S.C. 103 in view of the reference. * * *. The affidavit is interesting but irrelevant to the rejection since it is not directed to the subject matter "sought to be patented," namely, the use in the arts of the compounds. The obvious compound is not made less obvious by its properties in an art use. * * *. It appears that if an invention is present, it resides in the use of the claimed compounds as anti-inflammatory agents and should be claimed as such. Therefore, it is held that the subject matter of the claim is obvious in view of the reference and unpatentable thereover.

The applicant appealed to the board, which took no notice of the criticism that the invention should have been claimed as a "use." Before leaving this rejection, however, we make the observation that the ground of rejection seems to us somewhat confused, that it is un-

¹In this connection, see "The Forgotten Chemistry of the Hass-Henze Doctrine," by Bruce M. Collins, Journal of the Patent Office Society, April, 1962, Vol. XLIV, No. 4, page 284. Note also that in the first office action the examiner did not say that appellant's compounds are homologs of the Robins et al. compound XVI. He said, "The ethyl and n-butyl side chains * * * in applicant's claims * * * are obvious homologs of the methyl groups * * * in the reference * * *." [Emphasis ours.]

clear whether the affidavit was deemed truly *irrelevant* to the patentability of the claimed compounds, which alone were the "subject matter sought to be patented," and unclear to what extent, if any, obviousness of the compounds

[2] was predicated on the contention that the applicant should claim his invention as a process, which is the only way a "use" can be claimed. 35 U.S.C. 100(b) and 101. The last sentence of the above quotation seems to involve a non sequitur.

The examiner who made the above rejection next filed a very long and very argumentative Examiner's Answer, which reverts to the theme that appellant's "contribution" was not in the novel compounds claimed per se, "but rather in the newly discovered properties which are advantageous for a particular utility." Said the examiner:

Such contribution may properly be protected by claims to the mode of employing the compounds for their unexpected novel use, but does not support claims covering compounds which are structurally obvious and which also exhibit a family of properties and characteristics common to, and not differing significantly from, those of the homologue known and available to the prior art. An unexpected difference in a single property should not be adequate to support a claim for a novel, but obvious, homologue, which claim will dominate all properties and uses of the homologue, including those differing only in the expected manner from the known product.²

² It is noted that certain supposed facts are here being assumed. It is true that the applicant submitted proof as to only one unexpected, unobvious, beneficial property. The examiner's statements about the existence of a family of other properties common to the claimed compounds and the compound of the prior art finds support in the record, however, only on the basis of assumptions in turn based on assumed "homology." In his answer, the examiner cited a new reference, Wertheim "Textbook of Organic Chemistry" (2d Ed.), page 37 (1945). From it he quoted the following statement about members of "any one homologous series":

These compounds have similar chemical traits, because their structures are closely related; therefore we can learn the chemistry of the entire group with no more effort than would otherwise be required to study a single compound.

He had previously cited in his final rejection another new reference, Fieser and Fieser, "Organic Chemistry," 3d Ed. pages 30-31 (1956), which pages deal, so far as pertinent, only with the progressive relationships in the C_nH_{2n+2} homologous series,

This passage being only an expression of what might be termed the background sentiments of the examiner, the actual rejection was legally predicated by him on section 103 and its essence is contained in the following quotation:

In view of the known general relationship of homology, the disclosure of an organic chemical structure immediately suggests and renders obvious to the organic chemist of ordinary skill its homologues, as organic compounds. The homologous compound being obvious it is not seen how it can become less obvious, as a compound, merely by discovering that in addition to the community of common physical and chemical properties expected of members of an homologues [sic] series it also has other improved or valuable properties. Such discovery is not proper support for a patent for the compound per se. (In re Gauerke [24 CCPA 725, 86 F.2d 330] 31 USPQ 330 and the decisions *supra*).

We will dispose now of the Gauerke case, which has no bearing on the issue here. It held only that it was not a patentable invention to use in an old resin composition containing drying oil, sunflower seed oil, which was known, and known also to be a drying oil, in place of other drying oil formerly used. The court said that incorporating sunflower

with bare mention of similar relationships existing in the halogens: chlorine, bromine, and iodine.

Wertheim, at the point from which the above quotation was taken, was discussing the same "methane series of hydrocarbons" as Fieser and Fieser. The examiner stopped his quotation just before the sentence reading, "Of course we may anticipate certain 'exceptions' to this general rule, but such exceptions will make very little trouble." We are not here dealing with the methane series or with the type of "homology" which it illustrates.

[3] We have had sufficient contract with "homology" on this court to agree with the examiner that such similarity in structure as exists here probably indicates similarity in *some* undisclosed properties; but we are past giving too much legal significance to the bare term "homolog," even where there is an admission of homology, as there appears to be here. The term is often used loosely. So far as we know, the *assumed* similarities referred to by the examiner are of little or no practical or commercial significance. Certainly he has pointed to none. On the other hand, the *proven dissimilarity* is a matter of pharmacological significance, on which the examiner would be quite willing to grant a patent if the invention were claimed as a process. As to the other properties, nothing in the record gives us any information, not even the Robins et al. reference.

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seed oil in the resin was "a use which any one skilled in the art following the teachings of the prior art, might make of it." We are here concerned with the patentability of a new chemical compound having an inherent unknown, unobvious, pharmacologically advantageous property. Furthermore, nobody would be led by the prior art to use it for any purpose, so far as the record shows.

The Board Opinion

The Patent Office, for reasons undisclosed, convened a 5-man Board of Appeals to hear this case. It adopted a relatively long opinion (9 printed pages). We have tried as best we can to extract from it the essence of the board's reasons for denying patentability, taking into consideration the supporting brief filed by the Patent Office Solicitor. We believe the reasoning to be along these lines:

[4] 1. The section 103 requirement of unobviousness is no different in chemical cases than with respect to other categories of patentable inventions. (We would accept that, in principle.)

2. From the viewpoint of the organic chemist the structures of the claimed compounds would be "obvious" from the Robins et al. reference disclosure of the related trimethyl compound as well as from the disclosure of methylation by conventional methods, which would suggest to a chemist "the use of ethylating or other alkylating agent of short chain length" as a possibility.

3. Appellant relies on a *pharmacological* property as the significant characteristic.

4. The statutory unobviousness required of a claimed chemical compound to make it patentable must be "considered from a chemical viewpoint," i.e., from the viewpoint of chemists rather than pharmacologists, inasmuch as it is the chemists "who are involved with the synthesis of new compounds, and in their identification by physical characteristics and by reactions with other agents."

5. In conclusion the board said:

We have considered the facts in this case from the viewpoint of the chemist and find that the compounds would, without a shadow of doubt, be obvious to the chemist from the disclosure in the Robins et al. publication. In these circumstances, the showing made in the affidavit cannot be considered persuasive of patentability.

As in the case of the examiner's rejection, it is not clear from the above quotation whether or not the affidavit showing was ignored on the ground that

the compounds would be obvious to a chemist, or because it did not relate to "chemical" properties. The solicitor argues that the above quoted paragraph shows that the board "weighed the effect of the affidavit" but he also says that the board considered that the homologous relationship and the "chemical facts" made the claimed compounds "so obvious * * * that the showing of the affidavit was ineffective by itself to demonstrate the unobviousness of the claimed compounds." (Our emphasis.) Probably the best indication of how the board itself looked upon the affidavit is this paragraph from its opinion:

Such proof of advantages is not seen to occupy a different relationship than proof of commercial success or of the "filling of a long-felt want" often considered as sufficient to establish patentability in cases where some doubt of unobviousness exists, but which have been consistently held as insufficient alone to override the holding of unpatentability in a clear case of obviousness. [Emphasis added.]

In view of that statement, and since the board found the compounds to be obvious "without a shadow of doubt," we are bound to conclude that the board's process of reasoning was first to look at the compounds as chemists to see if they were obvious and, having no doubt that they were, it found no reason to consider the "pharmacological" facts shown by the affidavit, the existence of which facts has never been questioned. This conforms with the solicitor's oral argument which asked us to ignore the pharmacological properties on the ground that the claimed compounds were "so obvious."

Opinion

[5] The problem of "obviousness" under section 103 in determining the patentability of new and useful chemical compounds, or, as it is sometimes called, the problem of "chemical obviousness," is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. It is a problem of patent law.

[6] As everyone knows, section 103 is the statutory version of what was, prior to January 1, 1953, the effective date of the latest revision of the patent statutes, the judge-made requirement of "invention." We are not unaware that we are, in this case, in the field of what has come to be called the "Hass-Henze Doctrine," though the briefs do not men-

tion it by name.³ The Hass and Henze cases, which are mentioned, ante [7] date section 103 and suggest, by way of dicta, that proof of the existence of unobvious or unexpected beneficial properties in a new compound, which would otherwise appear to be obvious (along with its properties), is indicative of the presence of "invention" and hence of patentability. What this comes down to, in final analysis, is a rather simple proposition: If that which appears, at first blush, to be obvious though new is shown by evidence *not* to be obvious then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall. Many cases, both before and after the enactment of section 103, have been decided according to such reasoning and we shall now discuss a few of them.

Schering Corp. v. Gilbert, 153 F.2d 428, 68 USPQ 84 (CCA 2d), was decided in 1946. The claim sustained was to a specific chemical compound. It was proved to possess unobvious and highly useful properties as an X-ray contrast agent in cholecystography. The court characterized the claimed invention, "a short claim for one definite chemical compound not found in nature and never previously synthesized," as a "seemingly slight departure from the old." Its approach to the question of patentability was stated thus: (68 USPQ at 86):

* * * it is necessary to understand what the inventors did as well as what they sought to accomplish and give recognition to their end result as a novel and useful improvement, not in the art of organic chemistry but in that of cholecystography. [Emphasis added.]

In Parker v. Marzall, 92 F.Supp. 736, 86 USPQ 446, a suit under R. S. 4915

³ This "doctrine" was evolved by the bar from this court's opinions in the three cases called In re Hass et al., 31 CCPA 895, 903, 908, 141 F.2d 122, 127, 130, 60 USPQ 544, 548, 552, and in In re Henze, 37 CCPA 1009, 181 F.2d 196, 85 USPQ 261. See "The Hass-Henze Doctrine," by Alvin Guttag, Dec. 1961 JPOS, Vol. XLIII, No. 12, p. 808. This article commences with a discussion of what is meant by "homolog" and sets forth a definition which would exclude the compounds involved in the present case. In spite of all the talking and writing on the subject, we are not quite sure what the doctrine is but, whatever it is, insofar as the Hass and Henze cases are concerned, it appears to be based on dicta, since all of those cases affirmed the Patent Office rejections. For some observations on the limitations of homology, see In re Victor Mills, 47 CCPA 1135, 281 F.2d 218, 126 USPQ 513.

decided in 1950, the District Court for the District of Columbia entered, among others, the following findings of fact and conclusion of law after having filed an "Informal Memorandum." The findings of fact read (86 USPQ at 447):

7. The compound of plaintiffs' claim 2 is the next adjacent homologue of the compound of said Bayer and Dahlen [prior art] patents. [An ethyl substituent on a ring where the references had methyl.]

8. The compound of plaintiff's claim 3 is the next adjacent homologue of the compound of plaintiffs' claim 2 [ethyl in place of methyl as another ring substituent]. * * *

11. The evidence produced at the trial proves that the compounds claimed by the plaintiffs possess some unobvious and unexpected beneficial properties not possessed by the homologous compound disclosed in the prior art defense patents.

Conclusion of law:

2. In view of the evidence of unobvious unexpected and beneficial properties of the compounds of plaintiffs' claims 1, 2 and 3 not possessed by the homologous compound disclosed in the prior art, such claimed compounds constitute patentable invention. In re Hass et al., 141 F.2d 122, 60 USPQ 544, (CCPA 1944).

The unobvious advantages here involved were found in yellow azo pigments made from the claimed compounds as intermediates.

In In re Schechter et al., 40 CCPA 1009, 205 F.2d 185, 98 USPQ 144 (June 1953), this court reversed a rejection of claim 48 to a group of compounds (cyclopentenolones) which had been rejected as unpatentable over a prior art isomer. Biological function was taken into account in deciding in favor of patentability as shown by the following quotation (98 USPQ at 150):

We are convinced after a review of the record herein that, as appellants contend, there is a considerable degree of unpredictability in the insecticide field with homologs, isomers and analogs of known effective insecticides having proven ineffective as insecticides. In view of this, and the other factors previously discussed, we conclude that all the compounds of the subgroup in Markush claim 48 are inventive and patentable over the prior art of record, albeit they include isomers and homologs of the compounds shown in LaForge et al. Considering the history of the art at the time of the invention, and its success, we think such a conclusion unavoidable.

[8] Though the Patent Act just became effective and recognized its existence in section 112, no mention was made of section 103 or the necessity of inventiveness." The court was in terms of the requirement," its pre-revision equivalent respects. The court has stated, referring to In re other case, "We also indicated in the decisions held that homologs and isomers may if they are inventive over art compounds," citing Paizall, supra, with evident a

In Ruskin v. Watson, 123 101 USPQ 275, the District of Columbia decided the patentability of a compound structurally from a compound ready patented to the plaintiff the substitution of two ethyl groups for two hydrogen atoms in the compound was a therapeutic used to control muscular spasm, at page 276 of 101 USPQ with approval the following the opinion of this court in case (footnote 3, supra):

To those skilled in the art one homologue is not sufficient over an adjacent member of the series as requires inventiveness the beneficial properties of the new homologue lie clearly outside of the expectations which his science would inform a chemist should be inherent in the product.

Finding that the claimed product had been shown by evidence to be unobvious and unexpected beneficial properties not possessed by the prior art compound, the court rejected the rejection and held that the compound was patentably distinct.

⁴ [9] We are sure that our court in here referring to "those skilled in the chemical art" and to "chemists in the Henze case, using the term in any such narrow sense as that doing in the instant case, so as to biologists, pharmacologists, medical men, or any other competitive personnel who carry on investigations in the general field of drugs, toject matter being discussed in both prior art and claimed, whether compounds having, or alleged to be hypnotic, soporific or narcotic in character, the case went off on failure to prove that the claimed compound and the next homolog (in the strict sense of one -CH₂ group) did not have an advantageously high anticonvulsant effect with low toxicity which the extended would be expected.

[8] Though the Patent Act of 1952 had just become effective and the court recognized its existence in referring to section 112, no mention was made of section 103 or the necessity of finding "unobviousness." The court was still speaking in terms of the requirement of "invention," its pre-revision equivalent in most respects. The court had previously stated, referring to *In re Hass* and another case, "We also implicitly indicated in the decisions here cited that homologs and isomers may be patentable if they are inventive over known prior art compounds," citing *Parker v. Marzall*, *supra*, with evident approval.

In *Ruskin v. Watson*, 123 F.Supp. 33, 101 USPQ 275, the District Court for the District of Columbia decided in favor of patentability of a compound differing structurally from a compound already patented to the plaintiff only in the substitution of two ethyl groups in place of two hydrogen atoms. The compound was a therapeutic preparation used to control muscular spasm. The court, at page 276 of 101 USPQ, quoted with approval the following dictum from the opinion of this court in the *Henze* case (footnote 3, *supra*):

To those skilled in the chemical art, one homologue is not such an "advance" over an adjacent member of the series as requires invention, unless the beneficial properties realized in the new homologue lie clearly outside of the expectations which knowledge of his science would inform the trained chemist should be inherent in the product.⁴

Finding that the claimed product had been shown by evidence to possess unobvious and unexpected beneficial properties not possessed by the previous patented compound, the court disapproved of the rejection and held the two compounds patentably distinct.

* [9] We are sure that our predecessors in here referring to "those skilled in the chemical art" and to "chemists" were not, in the *Henze* case, using these terms in any such narrow sense as the board is doing in the instant case, so as to exclude biologists, pharmacologists, medical clinicians, or any other competent trained personnel who carry on investigative work in the general field of drugs, for the subject matter being discussed in that case, both prior art and claimed, was certain compounds having, or alleged to have, hypnotic, soporific or narcotic effect. The case went off on failure to prove that the claimed compound and the next adjacent homolog (in the strict sense of differing by one -CH₂ group) did not have the same advantageous high anticonvulsant activity with low toxicity which the examiner contended would be expected.

The same court in *Sterling Drug Inc. v. Watson*, 135 F.Supp. 173, 108 USPQ 37, gave judgment, in part, for plaintiff against the Commissioner of Patents in a suit under 35 U.S.C. 145 to obtain a patent on claims to levo-arterenol and dextro-arterenol. The prior art showed the racemic dl-arterenol and also the known next adjacent homologs of the claimed substances. The court found that "The evidence at the hearing abundantly supports the contention of the plaintiff that l-arterenol in the form here claimed has phenomenal therapeutic properties with respect to the treatment of irreversible shock and coronary occlusion. * * * These qualities are utterly unattainable either by the dl-compound, from which the pure l-arterenol is derived, or the admixture of l-arterenol with its homologues." The court said (108 USPQ at 38-39):

And there can hardly be any serious question that these beneficial characteristics were both unexpected and unobvious, which is the test to be applied in the matter of the patentability of a compound that is a homologue of another.

I have no hesitancy in reaching the firm conclusion that the l-arterenol * * * and the acid salt of l-arterenol * * * and the l-arterenol acid d-tartrate * * * are patentable. There is a difficulty with respect to claim 10, and that is that it also includes the claim to d-arterenol, and there has been no showing of any beneficial unexpected and unobvious properties of d-arterenol, and I, therefore, cannot conclude that d-arterenol is patentable.

It is interesting to observe here the applied principle working both ways. Where what we may call the apparent obviousness of the compound (including its properties) was overcome by evidence of unexpected advantageous properties the claim to it was held patentable; but where no such properties were shown to exist it remained an obvious compound with obvious properties.

In re Bergel et al., 48 CCPA 1102, 292 F.2d 955, 130 USPQ 206, involved, *inter alia*, claims to chemotherapeutic agents rejected as unpatentable over the prior art. As to the position of the Patent Office on the closeness of the claimed compounds to the prior art, the opinion of the court says (130 USPQ at 207):

The examiner states that the compound of claims 1 and 2 is "a chlorine analog" of the Harper et al. compound, by which he apparently means that a part of the hydrogen of the Harper

et al. compound is replaced by chlorine to form the claimed compounds. The examiner further noted that Everett et al. disclose compounds generally similar to those claimed by appellants and prepared by chlorination, and propose the use of such compounds in anti-tumor therapy.

In reversing the rejection the opinion says:

It is true that Harper et al. disclose compounds which, by the substitution of chlorine, a halogen, for part of the hydrogen, may be converted to the compounds recited in appealed claims 1 and 2, but, in our opinion, such conversion would not be obvious in the absence of any suggestion in the prior art as to why it should be made. [Emphasis added.]

And further (130 USPQ at 208):

The mere fact that it is possible to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination.

In re Larsen, 49 CCPA 711, 292 F.2d 531, 130 USPQ 209 (cert. denied, 133 USPQ 703), was an appeal taken only on process claims, claims to the product made by the process having been allowed. The appellant's arguments drew into consideration by the court, however, the patentability of the products, as to which Chief Judge Worley made the following observations (130 USPQ at 210) which are relevant here:

* * * the allowance of the claims to the compounds was based on the fact that they possessed unique, and presumably unexpected, properties. Since there was nothing to indicate that the compounds, when made, would have these properties, it was not obvious to make the compounds. In such a case the allowance of claims to the compounds must depend on the proposition that it was unobvious to conceive the idea of producing them, within the meaning of Title 35 U.S.C., Section 103. [Emphasis added.]⁵

⁵ None of the opinions in this case show, specifically, what the claimed compounds are useful for. The specification of the appealed application states the utility as follows:

My new compounds are useful as X-ray contrast agents and are particularly valuable for visualizing the bronchial tree (bronchography), and for

The writer, in a concurring opinion, made the following observation (130 USPQ at 213):

There is a certain amount of logic in holding a product to be unobvious because of the discovery in it of unobvious properties, such as its ability to act as a non-toxic X-ray contrast agent, because the properties inhere in the product. [Emphasis added.]

In re Lambooy, 49 CCPA 985, 300 F.2d 950, 133 USPQ 270, reversed the rejection of a single claim to an isoalloxazine compound. The decision was not handed down until after the briefs herein were filed. The only difference between the claimed compound and the prior art compound, riboflavin, was very much like the difference here—where riboflavin had two methyl groups, the claimed compound had two ethyl groups. It differed from riboflavin in a "pharmacological" property; where riboflavin acted in the animal body as a metabolite, the claimed compound, in spite of its "structural similarity," acted as an antimetabolite. Judge Martin, speaking for a unanimous court, said (133 USPQ at 274):

A comparison of the structural formulas of these two compounds shows clearly that there is substantial structural similarity. But more appears from the facts of this case than structural similarity, facts which raise genuine questions as to the real significance of such bare structural similarity, whatever label may be attached to it.

* * * There is no evidence in the record which would lead one skilled in this art to expect that the differences in molecular structure between riboflavin and appellant's compound would cause this difference in properties.

The next two quotations are so apt with respect to the arguments brought before us in the present case as to sound almost repetitious. We said in the Lambooy case:

The solicitor urges that "there is no specific evidence in the record of differences in chemical and physical properties of the prior art compound [riboflavin] and the claimed compound." In view of the bio-chemical differences which we have just discussed—

hepatolienography (visualization of the liver and spleen).

At least in the latter use the compounds would have to be ingested and to reach the liver and spleen by biological body processes. This is in the field of what the board deemed to be pharmacology rather than chemistry.

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At the most, we think this art would be taken into account in determining the patentability of the claimed compounds. The prior art can be attached to the claimed compounds by this fact is a noteworthy knowledge of an ordinary skill because it is true of all such structures. Though this is true to him, it does not mean that all new compounds should be obvious in the sense of the law. [Emphasis added.]

In re Petering and Fahey, 301 F.2d 676, 133 USPQ 271, concerned with compounds stated to have antimetabolite activity as antimetabolites. The rejection of claims 12 and 13 on art was reversed again speaking for a unanimous court, said (133 USPQ at 281):

Although it is also true that the specific compounds referred to in the record are rather similar to the compounds defined in claims 5, 11 and 13, there is a significant difference between a compound and Karrer's compound. [Emphasis added.]

We do not agree with the solicitor's argument that the compounds defined in claim 13 should not be considered in determining the patentability of the claimed compounds. The compounds are not within the scope of U.S.C. 102(b). In determining whether the claimed compounds are obvious within the scope of U.S.C. 103, we think that they may and should be considered having considered the factors which are convinced that the compounds are patentable over Karrer.

In that case, the board took essentially the same position as in the present case, saying, "we are convinced that the claimed compounds are patentable over Karrer."

cussed, we can only assume the solicitor is urging that while differences in chemical properties might be persuasive of patentability of the claimed compound, differences in biochemical [original emphasis] properties are not to be considered. We see no reason to distinguish between chemical and biochemical properties and no reason or authority for this position has been presented to us. [Emphasis added.]

* * *

At the most, we think one skilled in this art would be taught by the reference patents that other groups than those present in the riboflavin structure can be attached to the parent isalloxazine structure. We doubt that this fact is a noteworthy addition to the knowledge of an organic chemist of ordinary skill because he knows this is true of all such parent chemical structures. Though this would be obvious to him, it does not follow that all new compounds so produced would be obvious in the sense of the patent law. [Emphasis added.]

* * *

In re Petering and Fall, 49 CCPA 993, 301 F.2d 676, 133 USPQ 275, also dealt with compounds stated to have antimetabolite activity as riboflavin antagonists. The rejection of claims 5, 11, and 12 on art was reversed. Judge Martin, again speaking for a unanimous court, said (133 USPQ at 281):

Although it is also true that some of the specific compounds of Karrer [the reference] *** are structurally rather similar to the compounds defined in claims 5, 11 and 12, *** there is a significant difference in properties between appellants' compounds and Karrer's compounds. [Emphasis added.]

* * *

We do not agree with the board that the unexpected properties of the compounds defined in claims 5, 11 and 12 should not be considered in determining the patentability of these claims. The compounds are not described in Karrer within the meaning of 35 U.S.C. 102(b). In determining whether the claimed compounds are obvious within the meaning of 35 U.S.C. 103, we think their properties may and should be considered, and having considered the properties, we are convinced the compounds *** are patentable over Karrer.

In that case, the board had taken essentially the same position it took in the present case, saying, "we are not convinced that the ascertainment of the

property referred to could make such obvious compounds unobvious as compounds."

[10] From the foregoing cases it will be seen that this and other courts, both before and after the enactment of section 103, have determined the unobviousness and patentability of new chemical compounds by taking into consideration their biological or pharmacological properties. Nine of the ten cases above considered, directly and indirectly, involved such properties. Patentability has not been determined on the basis of the obviousness of structure alone. In fact, where patentability was found in the above cases it was found in spite of close similarity of chemical structure, often much closer similarity than we have here.

[11] Returning now to the decision of the board in this case, we think that it rests on one fundamental error of law, namely, the failure to take into consideration the biological or pharmaceutical property of the compounds as anti-inflammatory agents on the ground that to chemists the structure of the compounds would be so obvious as to be beyond doubt, and that a showing of such properties is to be used only to resolve doubt.

[12] From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify a plot of land, the thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.

The argument has been made that patentability is here being asserted only on the basis of one property, the anti-inflammatory activity, and that the compounds claimed and the compound of the prior art presumably have many properties in common. Presumably they do, but presumption is all we have here. The same is true of all of the compounds of the above cases which were held

patentable over compounds of the prior art, many of which must have had more in common by way of properties than the compounds here because the relationships, structurally, were even closer than here.

[13] As to the examiner's view that in a case such as this the applicant should claim his invention as a process utilizing the newly discovered property, the board appears to have ignored it, properly we think. It is contrary to practically all of the above decisions wherein no fault was found with granting product claims. Such claims have well-recognized advantages to those in the business of making and selling compounds, in contrast to process-of-use claims, because competitors in the sale of compounds are not generally users.

[14] The solicitor relies heavily on In re Finley and similar cases which we will now consider, arguing that there may be other factors to consider than a difference of a single advantageous property, which is true.

In re Finley, 36 CCPA 998, 174 F.2d 130, 81 USPQ 383 (1949), was an appeal on a single claim reading: "As a composition of matter, 2 ethyl hexyl salicylate." It was held unpatentable over several references which admittedly disclosed homologs and at least one isomer whose salts were all used as lubricant "additants," the same use disclosed for salts of the claimed compound. An affidavit was submitted in the case showing that the calcium salt of the claimed compound had two to three times the thermal stability as lubricant "additant" as the calcium salt of the prior art isomer n-octyl salicylate. The board held the tests made on the calcium salts too remote, affirming the examiner who had said:

But to assert that the property of the salt or of the oil is the property of the ester is clearly a confusion of the issue.

The passage in the Finley opinion relied on by the Patent Office is (81 USPQ at 386):

Obviously appellant construes our holding in those [Hass et al.] cases to mean that if a new and useful product does show unobvious or unexpected beneficial properties it follows that such a product is patentable. We did not affirmatively, or even by implication, so state in our decisions there. Our statement meant merely that unless a product does show the defined characteristics it is not patentable. Even if they be shown, the consideration of other factors may be required. As we said in our decision in the

second Hass et al. case, *supra*, "Whether novel chemical compounds are patentable over prior art isomers and homologues is a question to be determined in each case."

The principle of the above passage was also reiterated the next year in In re Henze, 37 CCPA 1009, 181 F.2d 196, 85 USPQ 261, in the following words (85 USPQ at 264-265):

Patentability is not resolved conclusively even where unexpected or unobvious beneficial properties are established to exist in novel members of a homologous series over prior art members, as the circumstances of the case may require a consideration of other factors. [citing Finley] A mere difference in degree is not the marked superiority which ordinarily will remove the unpatentability of adjacent homologues of old substances. In re Loring Coes, Jr., *supra* [36 CCPA 1067, 173 F.2d 1012, 81 USPQ 369]. [Emphasis added.]

In the Loring Coes case the invention was an abrasive grinding wheel. It was specifically found that "the improvement, if any, is one of degree viewed only from a single aspect." The new grinding wheel was shown to wear longer, but the old wheel was shown to be more efficient in the amount of metal removed per unit of time. The invention related to the synthetic resin binder in the wheel which differed only slightly in composition from prior resin binders, the difference residing only in the hardening agent used. The hardener selected differed from a known prior art hardening agent only by the omission of one -CH₂ group out of six, found in triglycol dichloride, and was held to be an unpatentable selection.

The other factor of importance which was present in the Finley, Henze, and Coes cases and others of their type is that the prior art disclosure was not merely of a structurally similar compound but also, at least to a degree, of the same desired property relied on for patentability in the new compound. Such an "other factor" must of course be considered because it bears on the obviousness of the compound, which is, realistically and legally, a composite of both structure and properties.

As should be apparent from the foregoing, we regard the board's opinion and decision as contrary to well established law. We see no reason to change that law. The decision is therefore reversed.

WORLEY, Chief Judge, concurs in result only.

50 CCPA 1142

Court of Customs and Pat.

LIBRASCOPE, INCORPORATED

LIBRASCOPE DIVISION GENE

SION, INC.) v. LIBRAPHO

Appl. No. 6883 Decided M

Rehearing denied May

TRADEMARKS

1. Identity and similarity—symbols (§ 67.413)

"Libraphone" in association showing row of books a sign showing row of books a of speaker so resembles as to be likely to cause conf

2. Identity and similarity—mined—Prior decisions

While prior decisions ust little value in determining l confusion between marks, in must be analyzed as court case.

3. Identity and similarity—terminated — Doubt ag comers (§ 67.4067) - -

Doubts as to likelihood o between marks should b against newcomer.

Appeal from Trademark Appeal Board of the Patent USPQ 76.

Trademark opposition No. Librascope, Incorporated (Librascope Division General Inc.) against Libraphone, Ir tion, Serial No. 35,661, file 1957. From decision dismiss ion, opposer appeals. Reverse Judge, dissenting with opinic Worley, Chief Judge, joins.

THEODORE H. LASSAGNE, Gler and JAS. M. NAYLOR and NEAL, both of San Franc for appellant.

CHARLES R. ALLEN, JR., D.C., for appellee.

Before WORLEY, Chief Judge MARTIN, SMITH, and ALMO ate Judges.

SMITH, Judge.

This is an appeal from the the Trademark Trial and Ap 131 USPQ 76, which dismis lant's opposition to appellee tion¹ for registration of "Libraphone" in association sign showing a row of book horn portion of a speaker. T

¹ Ser. No. 35,661, filed Aug. 16

**U.S. Court of Appeals
Federal Circuit**

**Genentech Inc. v. The Wellcome Foundation
Ltd.**

Nos. 92-1503, -1505

Decided June 27, 1994

PATENTS

1. Patent construction — Claims — In general (§125.1301)

Specific activity limitation which appears in claims of one of three patents in suit relating to production of protein tissue plasminogen activator cannot be considered to be inherent in phrase "human tissue plasminogen activator" which appears in other two patents in suit, since there is no basis in specifications and prosecution histories of those two patents for reading specific activity limitation into phrase, since those patents were researched and prosecuted by different entities, and since specific activity concept is critical to patentability of first patent but not to other two, in which other limitations serve to distinguish claimed subject matter over prior art.

2. Patent construction — Claims — Defining terms (§125.1305)

Phrase "human tissue plasminogen activator" means tissue plasminogen activator produced through recombinant DNA technology but having same structure as natural t-PA, which is narrow structural definition set forth in specification, even though specification also provides three other definitions, since such narrow definition is most consistent with limited forms in which claims are drafted.

3. Infringement — Doctrine of equivalents — In general (§120.0701)

"Function," of human tissue plasminogen activator, for purposes of applying function-way-result equivalency test, is catalyzing conversion of plasminogen to plasmin and binding to fibrin, rather than broad definition of stimulating dissolution of fibrin clots through cleavage of plasminogen to plasmin.

Particular patents — Chemical — Plasminogen activators

4,752,603, Collen, Rijken, and Matsuo, plasminogen activator and pharmaceutical composition having thrombolytic activity, not infringed under doctrine of equivalents.

4,766,075, Goeddel, Kohr, Pennica, and Vehar, human tissue plasminogen activator, not infringed under doctrine of equivalents.

4,853,330, Goeddel, Kohr, Pennica, and Vehar, human tissue plasminogen activator, not infringed under doctrine of equivalents.

Appeal from the U.S. District Court for the District of Delaware, Farnan, J.; 24 USPQ2d 1782.

Action by Genentech Inc., Innovi N.V. and Leuven Research & Development VZW against The Wellcome Foundation Ltd., Wellcome Biotechnology Ltd., Burroughs Wellcome Co., B.W. Manufacturing Inc., Welgen Manufacturing Inc., Genetics Institute Inc. and GI Manufacturing Inc. for patent infringement. From federal district court's denial of defendants' motion for judgment as a matter of law, defendants Genetics Institute Inc. and GI Manufacturing Inc. appeal. Reversed; Lourie, J., concurring in separate opinion.

Stephen F. Sherry, Allegretti & Witcoff, Chicago, Ill., and D. Dennis Allegretti, of Allegretti & Witcoff, Boston, Mass., for plaintiffs.

James L. Quarles III, of Hale & Dorr, Washington, D.C.; Bruce M. Eisen and Steven R. Lazar, Genetics Institute Inc., Cambridge, Mass.; and Stanley H. Lieberstein and Edward A. Meilman, of Ostromolenk, Faber, Gerb & Soffen, New York, N.Y., for defendants.

Before Plager and Lourie, circuit judges, and Cowen, senior circuit judge.

Plager, J.

The question in this patent infringement action is whether a protein, formed through recombinant DNA technology, infringes, under the doctrine of equivalents, any of three patents: a patent directed to a natural protein extracted from certain human cancer cells; a patent directed to the materials needed to produce the natural protein through recombinant DNA technology, i.e., the DNA sequence encoding the protein, the expression vector containing the sequence, and the microorganism or cell culture capable of expressing the protein; or a patent directed to the process of producing the natural protein through recombinant DNA technology. The United States District Court for the District of Delaware found in favor of the patent owners/licensees (and their agent), plaintiff's Genentech, Inc. (Genentech), Innovi N.V. (Innovi), and Leuven Research & Development VZW (Leuven), holding that the Genetics defendants, to wit, Genetics Institute, Inc. (Institute) and Genetics Man-

ufacturing, Inc. (GI Manufacturing), infringed under the doctrine of equivalents U.S. Patent Nos. 4,752,603 (the '603 patent), 4,766,075 (the '075 patent), and 4,853,330 (the '330 patent). That judgment was entered by the court on April 6, 1990 in consolidated Civil Action Nos. 88-330 and 88-407 following a jury trial, and became final on July 15, 1992 when the court denied defendants' motions for judgment as a matter of law (JMOL)¹ or, in the alternative, a new trial. *Genentech Inc. v. Wellcome Foundation Ltd.*, 798 F. Supp. 213, 24 USPQ2d 1782 (D. Del. 1992). The Genetics defendants appeal. We find that the judgment of the trial court is not sustainable under the law, and reverse.

BACKGROUND

1.

The protein tissue plasminogen activator (t-PA) plays an important role in the dissolution of fibrin clots in the human body. The body forms such clots typically to breach a rupture in a blood vessel. When they are no longer needed, they are dissolved through the action of plasmin, an enzyme which binds to the fibrin and severs the bonds between the fibrin molecules. Since plasmin circulates through the blood in an inactive form called plasminogen, a mechanism must be provided to activate the plasminogen and convert it to plasmin when a clot is targeted for dissolution by the body. The protein t-PA serves as that mechanism.

Unfortunately, a pathological clot known as a 'thrombus' sometimes forms in intact vessels and causes life-threatening conditions. When a thrombus occurs, the normal amount of t-PA circulating in the body may not be effective to produce plasmin fast enough to dissolve the clot, and avoid the risk of heart muscle damage or death. An additional dosage of a material which activates the plasminogen is often necessary to dissolve the clot rapidly. Several materials, such as natural t-PA extracted from human cells, streptokinase, or urokinase, were known to perform this function, although imperfectly, either because, in the case of streptokinase and urokinase, of undesirable side effects and low affinity to fibrin, and in the case of natural t-PA, the inability to derive clinically effective volumes from known sources.

¹ In 1991, pursuant to an amendment to Rule 50 of the Federal Rules of Civil Procedure, the former judgment notwithstanding the verdict (JNOV) was changed to a motion for JMOL.

Plaintiff Leuven then set to work to find a way to produce natural t-PA in a commercially useful way, i.e., in sufficient quantities and at a sufficient level of purity and effectiveness to meet commercial demands. This task was assigned to three of Leuven's scientists — Drs. Collen, Rijken, and Matsuo. They discovered that a commercially useful quantity and purity of natural t-PA could be produced from human melanoma cell cultures.

This discovery is the subject of the '603 patent, the sole independent claim of which reads:

1. Human plasminogen activator, having thrombolytic properties, immunologically distinct from urokinase and having a specific activity of about 500,000 IU/mg. using the WHO First International Reference Preparation of t-PA (tissue plasminogen activator) as assay standard or a specific activity of about 90,000 IU/mg. using the WHO First International Reference Preparation of urokinase as assay standard.

Meanwhile, plaintiff Genentech set about pursuing the same objective, a commercially useful process for producing natural t-PA, but by a different route — recombinant DNA technology.² That task was assigned to four Genentech scientists — Drs. Goeddel, Kohr, Vehar, and Pennica. They ultimately discovered such a process as well as the intermediate products used in the process, i.e., the DNA sequence encoding human t-PA, the expression vector containing that sequence, and the microorganism or cell culture capable of expressing human t-PA using that vector.

The intermediate products are the subject of the claims of the '075 patent, of which claims 1, 3, and 8 are representative:

1. A DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator.

* * *

3. A recombinant expression vector containing a DNA sequence encoding human tissue plasminogen activator, wherein the vector is capable of expressing human tissue plasminogen activator in a transformed microorganism or cell culture.

* * *

8. A cell culture capable of expressing human tissue plasminogen activator, obtained by transforming a mammalian cell line with a vector according to claim 3.

² For a useful background on the subject, the reader is referred to Karl Drlica, *Understanding DNA and Gene Cloning: A Guide for the Curious* (1984).

The processes claims of the 8, and 12 are

1. A process DNA sequence plasminogen host cell, said microorganism formed with said DNA

8. A process human tissue comprising:
(a) growing medium, said or cell culture vector man tissue
(b) simultaneously thereby produced tissue plasm

12. A process human tissue comprising:
(a) transforming culture with DNA encoding activator; and
(b) expressing formed microorganism

The plaintiff Leuven, the owner of the technology, the owner and the exclusive licensee of Innova, Ltd., licensing its technology in this action on January 1, 1988, issued, the '603 patent, and filed a complaint after August 23, 1988, that patent. On August 1, 1988, a rate action against the infringement of subsequently claimed

The original Genetics defendant — Manufacturing defendants — Ltd. (Foundation Ltd. (Biotechnology Co. (Burroughs (BW Manufac

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The process itself is the subject of the claims of the '330 patent, of which claims 1, 8, and 12 are representative:

1. A process which comprises expressing a DNA sequence encoding human tissue plasminogen activator in a recombinant host cell, said recombinant host cell being a microorganism or cell culture transformed with an expression vector containing said DNA sequence.

8. A process for producing recombinant human tissue plasminogen activator comprising:

(a) growing recombinant cells in a growth medium, said cells being a microorganism or cell culture transformed with an expression vector containing DNA encoding human tissue plasminogen activator; and
(b) simultaneously expressing said DNA, thereby producing recombinant human tissue plasminogen activator.

12. A process for producing recombinant human tissue plasminogen activator comprising:

(a) transforming a microorganism or cell culture with a replicable vector containing DNA encoding human tissue plasminogen activator; and
(b) expressing said DNA in said transformed microorganism or cell culture.

2.

The plaintiffs in this action consist of Leuven, the owner of the '603 patent; Genentech, the owner of the '075 and '330 patents, and the exclusive licensee of the '603 patent; and Innovi, Leuven's agent to assist it in licensing its technology rights. They initiated this action on June 21, 1988, the day the '603 patent issued, alleging infringement of the '603 patent, and subsequently amended their complaint after the '075 patent issued on August 23, 1988 to allege infringement of that patent. When the '330 patent issued on August 1, 1989, plaintiffs initiated a separate action against defendants alleging infringement of that patent; that action was subsequently consolidated with the other.

The original defendants consisted of the Genetics defendants — Institute and GI Manufacturing — as well as the Wellcome defendants — The Wellcome Foundation Ltd. (Foundation); Wellcome Biotechnology Ltd. (Biotechnology); Burroughs Wellcome Co. (Burroughs); BW Manufacturing, Inc. (BW Manufacturing); and WelGen Manu-

facturing, Inc. (WelGen).¹ GI Manufacturing is a wholly-owned subsidiary of Institute. BW Manufacturing is a wholly-owned subsidiary of Burroughs, which in turn is a wholly-owned subsidiary of Foundation. GI Manufacturing and BW Manufacturing jointly own WelGen. That entity was, at the time this action was initiated, admittedly constructing a facility in the United States for the commercial production of t-PA.

According to plaintiffs' allegations, the Genetics and Wellcome defendants acted in concert to make, use, and import into the United States natural t-PA, or variants of natural t-PA, produced through recombinant DNA technology that infringe the patents-in-suit. There are two accused products — met-t-PA and FE1X — both of which are structurally distinct from natural t-PA.² The Genetics defendants are alleged to have manufactured in the United States the FE1X product for commercial purposes. The Wellcome defendants are alleged to have manufactured in the United Kingdom the met-t-PA product, and imported that product into the United States for commercial purposes.

In response to plaintiffs' allegations, defendants denied infringement and asserted the affirmative defenses that the three patents-in-suit were invalid, and unenforceable due to inequitable and fraudulent conduct during prosecution. Defendants also asserted counterclaims alleging that plaintiffs' procurement and enforcement of the three patents-in-suit against them constituted an antitrust violation and unfair competition.

The parties then filed cross-motions for summary judgment on the infringement

¹ As discussed further in this opinion, the Wellcome defendants are no longer parties to this action.

² The amino acid sequence of natural t-PA consists of five separate domains or regions each having different functional attributes: the Finger (F) region, the Epidermal Growth (E) region, the Kringle 1 (K1) region, the Kringle 2 (K2) region, and the Serine Protease (P) region. The amino acid sequence of met-t-PA is the same length as that of natural t-PA, but differs from that sequence through an amino acid substitution at position 245 of the K2 region (where methionine is substituted for valine). The FE1X protein takes its name from the fact that it lacks the Finger (F) region and most of the Epidermal Growth (E) region of natural t-PA, and eliminates one of the carbohydrate chains by altering the gene at position 117 of the K1 region (where glutamine is substituted for arginine), thereby changing the glycosylation pattern (1X). It also has a different amino acid at position 245 (the same substitution as met-t-PA). It is undisputed that neither met-t-PA or FE1X naturally occur in humans.

question in relation to the '603 and '075 patents. The '330 patent was not the subject of those motions. Shortly before trial was to commence, on March 8, 1990, the court granted defendants' motions in part. Specifically, it found that the accused products did not literally infringe the '603 and '075 patents, but it reserved the doctrine of equivalents issue for trial. *Genentech Inc. v. The Wellcome Foundation Ltd.*, 14 USPQ2d 1363 (D. Del. 1990). In concluding that defendants' products did not literally infringe the '603 and '075 patents, the court focused on the "human plasminogen activator" limitation recited in the '603 claims and the "human tissue plasminogen activator" limitation appearing in the '075 claims. It interpreted these phrases to mean the full length amino acid sequence of human t-PA plus any "naturally-occurring allelic variant" thereof. *Id.* at 1369. Since neither of the accused products contains the full length sequence of natural t-PA or any naturally-occurring variant thereof, the court concluded they did not literally meet that limitation. *Id.* at 1369-70.

The court also focussed on the "specific activity of about 500,000 IU/mg." limitation recited in the '603 claims. Although that limitation is not expressly recited in the '075 claims, the court found it was implicit in those claims. *Id.* at 1368. Based on representations made to the United States Patent and Trademark Office (PTO) during the '603 prosecution, the court interpreted that phrase to mean something "significantly above" a specific activity of about 266,000 IU/mg., to distinguish the '603 claims from prior work of one of the '603 inventors, Dr. Rijken, in which natural t-PA with a specific activity of 266,000 IU/mg. had been isolated. *Id.* at 1368. It found that that limitation was likewise not literally met by either of the accused products, FEIX, because of plaintiff's failure to prove the specific activity level of that product, and met-t-PA, because the proven specific activity level was not "about 500,000 IU/mg.". *Id.* at 1369-70.

Subsequently, on March 15, 1990, the court commenced a jury trial on the doctrine of equivalents issue. After 15 days of testimony, the trial court instructed the jury. Although the court issued general instructions on the issues of claim construction, the doctrine of equivalents, and prosecution history estoppel, the court refused defendants' request that the court instruct the jury on the construction and interpretation of the claims it had previously utilized in resolving the literal infringement issue.

After deliberating for two hours and forty-eight minutes, the jury returned special

verdicts finding that (1) the accused product manufactured by the Wellcome defendants — met-t-PA — infringed under the doctrine of equivalents the '603 and '330 patents; (2) the accused product manufactured by the Genetics defendants — FEIX — infringed under the doctrine of equivalents the '603, '075, and '330 patents;³ and (3) all three patents were not proved invalid or unenforceable. In addition, the jury determined that defendants had not shown plaintiffs committed antitrust violations or unfair competition. On April 6, 1990, the court entered judgment in accordance with the jury's special verdicts.

On April 20, 1990, defendants filed their motions for JMOL or, in the alternative, for a new trial. Some two years later, in the decision that gave rise to this appeal, the trial court denied those motions. The Genetics defendants then filed this appeal. One of the Wellcome defendants — WelGen, the joint venture — also appealed; however, on October 22, 1992, it dismissed its appeal with prejudice. None of the other Wellcome defendants appealed. While this appeal was pending, the Wellcome defendants announced their intention to discontinue development of a t-PA product. Thus the issue of infringement by met-t-PA is not involved in this appeal. Nor did plaintiffs/appellees cross-appeal the partial summary judgment against them on the literal infringement question. The only issues now on appeal then are whether FEIX infringes one or more of the '603, '075, or '330 patents under the doctrine of equivalents.

DISCUSSION

The Genetics defendants state three separate grounds upon which they assert that the judgment of the trial court should be reversed. First, there was a lack of substantial evidence showing that FEIX met under the doctrine of equivalents the specific activity limitation expressly recited in the '603 claims and implicit in the claims of the other two patents-in-suit. Second, there was a failure to provide particularized testimony sufficient to support the equivalence finding in relation to the "human tissue plasminogen activator" limitation recited in the '075 and '330 claims as required by *Malta v. Schumerich Carrilons, Inc.*, 952 F.2d 1320, 21 USPQ2d 1161 (Fed. Cir. 1991), cert. denied, 112 S. Ct. 2942 (1992). Third, there

³ The specific claims that were found infringed were claim 1 of the '603 patent, claim 8 of the '075 patent, and claim 8 of the '330 patent.

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In the alterr state four sepa assert they are the jury was n — including : the constructi '603 and '075 in resolving on infringement patents — wi doctrine of e. jury was not quences to de fringement. T prosecution hi relating to t British courts the patents-in cluded. Fourt great weight o research and biotechnology

Before addr sary to resolve construction whether, as t the specific ac the '603 claim '330 claims. S ics defendant figure appeari means 500.00 the bovine fibi the literal me tissue plasmin the '075 and issues of law claim constr claims mean. v. American 1575, 28 US 1993), cert. (1994); Johns

' As we have of patent infri E.g., Lemelson 1202, 1206, 23 1992), cert. den claim must be i scope and me mined whether within the soc claim. *Id.*; N American Cyan USPQ2d 1333, nied. 128 L.Ed. v. Cardiac Res 1578, 6 USPQ2

accused product defendants assert the doctrine of equivalents. (2) factured by the '603, and (3) all three defendants determined that plaintiffs committed unfair competition. It entered judgment on the jury's special

plaintiffs filed their alternative, four years later, in the appeal, the trial court. The Genetics defendants appealed. One of the defendants, the joint venture, on October 1, 1990, its appeal with the Wellcome defendants against the Wellcome defendants' appeal was dismissed. Thus the issue of infringement is not involved in this appeal. However, on appeal then one or more of the defendants under the

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state three separately assert that the court should be re-ack of substantial infringement under the specific activity limitation in the '603 claims of the other, there was a failed testimony sufficiency finding in issue plasminogen and in the '075 and '330 patents. *Malta v. Schulz*, 152 F.2d 1320, 21 (1991), cert. denied, 1992. Third, there

it were found in the '603 patent, claim 8 of the '330 patent.

was a complete absence of proof of any involvement by GI Manufacturing in infringing activity.

In the alternative, the Genetics defendants state four separate grounds upon which they assert they are entitled to a new trial. First, the jury was not provided sufficient guidance — including an instruction informing it of the construction and interpretation of the '603 and '075 claims the court had adopted in resolving on summary judgment the literal infringement question in relation to those patents — with which to fairly resolve the doctrine of equivalents issue. Second, the jury was not advised of the adverse consequences to defendants of a finding of infringement. Third, relevant portions of the prosecution histories of the patents-in-suit — relating to the treatment received in the British courts by the British counterparts of the patents-in-suit — were improperly excluded. Fourth, the verdict is against the great weight of the evidence and would stifle research and development in the field of biotechnology.

Before addressing these points, it is necessary to resolve three threshold issues of claim construction or interpretation.⁴ First, whether, as the Genetics defendants assert, the specific activity limitation appearing in the '603 claims is implicit in the '075 and '330 claims. Second, whether, as the Genetics defendants further assert, the 500,000 figure appearing as part of that limitation means 500,000 IU/mg. as measured using the bovine fibrin plate assay. Third, what is the literal meaning of the phrase "human tissue plasminogen activator" appearing in the '075 and '330 claims. These issues are issues of law — they are classic issues of claim construction, that is, what do the claims mean. See *North American Vaccine Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1575, 28 USPQ2d 1333, 1336 (Fed. Cir. 1993), cert. denied, 128 L.Ed. 2d 365 (1994); *Johnston v. IVAC Corp.*, 885 F.2d

⁴ As we have repeatedly said, a determination of patent infringement is a two-step analysis. E.g., *Lemelson v. General Mills Inc.*, 968 F.2d 1202, 1206, 23 USPQ2d 1284, 1287 (Fed. Cir. 1992), cert. denied, 113 S.Ct. 976 (1993). First, a claim must be interpreted to determine its proper scope and meaning; second, it must be determined whether an accused device or process is within the scope of the properly interpreted claim. *Id.*; *North American Vaccine Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1574, 28 USPQ2d 1333, 1335 (Fed. Cir. 1993), cert. denied, 128 L.Ed.2d 365 (1994) (citing *ZMI Corp. v. Cardiac Resuscitator Corp.*, 844 F.2d 1576, 1578, 6 USPQ2d 1557, 1559 (Fed. Cir. 1988)).

1574, 1579-80, 12 USPQ2d 1382, 1385-86 (Fed. Cir. 1989). They are for the court to decide and explicate on the record. See *Read Corp. v. Portec Inc.*, 970 F.2d 816, 822, 23 USPQ2d 1426, 1432 (Fed. Cir. 1992). Since the trial court did not instruct the jury on these issues, and did not appear to have utilized its prior claim interpretation in ruling on the motions for JMOL, it is necessary for us to resolve these issues now in ruling on the court's denial of Genetics' motions for JMOL. *Id.* at 822-23, 23 USPQ2d at 1432. We address each of these threshold points in order.

3. Claim Construction

a. The specific activity limitation

We begin with the question of whether, as the Genetics defendants assert, the specific activity limitation appearing in the '603 claims is implicit in the '075 and '330 claims.

The Genetics defendants first assert that plaintiffs/appellees are precluded from arguing that the limitation is not implicit in those claims due to plaintiffs' failure to appeal the district court's grant of summary judgment (by filing a cross-appeal to the present appeal). As noted previously, in that decision, the trial court determined that the limitation was implicit in the '075 claims. Thus, according to the Genetics defendants, that determination is "law of the case."

We disagree. "The general rule is that, without taking a cross-appeal, the prevailing party may present any argument that supports the judgment in its favor." *Radio Steel & Mfg. Co. v. MTD Products, Inc.*, 731 F.2d 840, 843, 221 USPQ 657, 660 (Fed. Cir.), cert. denied, 469 U.S. 831 (1984); see 9 James W. Moore, *Moore's Federal Practice*, ¶ 204.11[3], at 4-47 (2d ed. 1993). Here, were we to adopt a claim construction more favorable to plaintiffs' case than the construction adopted by the district court on summary judgment, that would have no different result than affirmance of the trial court's April 6, 1990 judgment. Accordingly, plaintiffs are not precluded from arguing a construction in support of the judgment that is different from that announced by the trial court.

[1] In any event, the Genetics defendants argue, the specific activity limitation appearing in the '603 claims is inherent in the

"[L]aw of the case phrases are occasionally used to describe the consequences of failure to appeal an issue or to preserve it for appeal." See 18 Charles A. Wright et al., *Federal Practice and Procedure*, §4478, at 788 (1981).

phrase "human tissue plasminogen activator" appearing in the '075 and '330 claims. Again, we disagree. Assuming for the sake of argument that the phrase "human tissue plasminogen activator" is ambiguous, there is no basis in the '330 and '075 specifications and prosecution histories for reading a specific activity limitation into the phrase. The only evidence identified by the Genetics defendants as a plausible basis for doing so is the '603 specification and prosecution history. However, that patent is completely unrelated to the '330 and '075 patents. It was prosecuted by a different entity than the others. The underlying research was conducted by different individuals than the research underlying the others. And finally, while the specific activity concept is a definition of purity critical to the patentability of the '603 claims — it is the critical distinction of those claims over the less purified materials constituting the relevant prior art⁹ — the same cannot be said of the '330 and '075 claims, in which other limitations serve to distinguish the claimed subject matter over the prior art. Thus, that documentation cannot serve as the basis for reading the limitation into the phrase. We conclude that the '330 and '075 patents contain no implied specific activity limitation. The avoidance of this limitation by FEI X thus cannot provide the basis for a finding of non-infringement under the doctrine of equivalents in relation to these patents.

b. The meaning of "500,000 IU/mg."

The next question to resolve is the meaning of the numerical figure "500,000 IU/mg." appearing as part of the specific activity limitation of the '603 claims. The Genetics defendants argue that the figure means 500,000 IU/mg. as measured using a bovine fibrin plate assay. The plaintiffs, by contrast, argue that the figure is not limited to any specific assay type.

We agree with the Genetics defendants. According to the prior art of record, the numerical measurement of specific activity of t-PA can vary by more than a factor of three depending on the specific assay used.¹⁰ Thus, in order for the 500,000 figure to serve

⁹ That phrase was added to the '603 claims to distinguish over prior work of one of the '603 inventors, Dr. Rijken, in which natural t-PA with a specific activity level of 266,000 IU/mg. had been isolated.

¹⁰ Dingeman C. Rijken et al., *Purification and Partial Characterization of Plasminogen Activator from Human Uterine Tissue*, 580 *Biochimica et Biophysica Acta* 140, 147-48 (1979).

its intended purpose of distinguishing over the prior art value of 266,000 IU/mg., it is necessary to assign that figure a specific assay type. Since the claim is silent on this point¹¹, we must look elsewhere for the answer. See *Hormone Research Found. v. Genentech, Inc.*, 904 F.2d 1558, 1562, 15 USPQ2d 1039, 1043 (Fed. Cir. 1990), cert. dismissed, 499 U.S. 955 (1991).

The '603 prosecution history reveals that the 500,000 figure was added to the '603 claims during prosecution to distinguish over prior work of Dr. Rijken's. That work had resulted in a specific activity of 48,000 IU/mg., when expressed in terms of the prevailing urokinase standard, and 266,000 IU/mg., when expressed in terms of the new and preferred t-PA standard that had evolved after the '603 filing date.¹²

The specific activity of the claimed product was initially only available in terms of the urokinase standard. When so expressed, the figure was 90,000 IU/mg. Dr. Collen was assigned the task of expressing the figure in terms of the new standard. That work resulted in the 500,000 figure. An article contained in the '603 prosecution history shows that this figure was determined using "bovine fibrin films", i.e., a bovine fibrin plate assay.¹³ Apparently, that assay was used so that the figure would be compatible with Dr. Rijken's prior work, in which specific activity was measured using the bovine fibrin plate assay¹⁴, and with the work which gave rise to the filing of the '603 patent, in which specific activity was likewise measured using the bovine fibrin plate assay. Col. 5, ll. 1 - 6. Accordingly, we conclude that the 500,000 figure means IU/mg. as measured using the bovine fibrin plate assay.

c. The definition of "human tissue plasminogen activator"

We next address the question of the meaning of the phrase "human tissue plasminogen

¹⁰ Although the claim does refer to an international assay standard — the WHO International Reference Preparation of t-PA — that is a concept distinct from assay type.

¹¹ Dingeman C. Rijken, *Purification and Characterization of the Plasminogen Activator Secreted by Human Melanoma Cells in Culture*, 256 *J. Biological Chemistry* 7035, 7040 (1981).

¹² P. Holovet et al., *Measurement of Free, One-Chain Tissue-Type Plasminogen Activator in Human Plasma With an Enzyme-Linked Immunosorbent Assay Based on an Active Site-Specific Murine Monoclonal Antibody*, 69 *Blood* 284, 284 (1987).

¹³ Rijken, *supra* note 11, at 7036.

"activator" appears in the '603 claims. Since the term cannot be explicitly defined by itself, we look elsewhere for its meaning. See *McFarland v. Genentech, Inc.*, 666 F.2d 1562, 15 USPQ2d 1039, 1043 (Fed. Cir. 1984), cert. dismissed, 499 U.S. 955 (1991).

A problem arises in that at least four possible definitions are set forth in the '603 claims during prosecution to distinguish over prior work of Dr. Rijken's. That work had resulted in a specific activity of 48,000 IU/mg., when expressed in terms of the prevailing urokinase standard, and 266,000 IU/mg., when expressed in terms of the new and preferred t-PA standard that had evolved after the '603 filing date.¹¹

¹⁴ We use the term "tissue plasminogen activator" to refer to the specific enzyme that is found in the extracellular fluid of various tissues. This enzyme is secreted by various cells, including fibroblasts, endothelial cells, and leukocytes. It is also found in the blood plasma and serum. The term "tissue plasminogen activator" is often used interchangeably with the term "plasminogen activator".

¹⁵ Plaintiffs' definition of "tissue plasminogen activator" is broader than the term "tissue plasminogen activator" as used by the prior art. The term "tissue plasminogen activator" as used by the prior art refers to a specific enzyme that is found in the extracellular fluid of various tissues. This enzyme is secreted by various cells, including fibroblasts, endothelial cells, and leukocytes. It is also found in the blood plasma and serum. The term "tissue plasminogen activator" is often used interchangeably with the term "plasminogen activator".

¹⁶ Specifically, the term "tissue plasminogen activator" as used by the prior art refers to a specific enzyme that is found in the extracellular fluid of various tissues. This enzyme is secreted by various cells, including fibroblasts, endothelial cells, and leukocytes. It is also found in the blood plasma and serum. The term "tissue plasminogen activator" is often used interchangeably with the term "plasminogen activator".

¹⁷ The specific meaning of the term "tissue plasminogen activator" as used by the prior art is that it means the enzyme that is found in the extracellular fluid of various tissues. This enzyme is secreted by various cells, including fibroblasts, endothelial cells, and leukocytes. It is also found in the blood plasma and serum. The term "tissue plasminogen activator" is often used interchangeably with the term "plasminogen activator".

¹⁸ Specifically, the term "tissue plasminogen activator" as used by the prior art refers to a specific enzyme that is found in the extracellular fluid of various tissues. This enzyme is secreted by various cells, including fibroblasts, endothelial cells, and leukocytes. It is also found in the blood plasma and serum. The term "tissue plasminogen activator" is often used interchangeably with the term "plasminogen activator".

All such activities resulting in the production of plasminogen activator are described as being "tissue plasminogen activator" activities.

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activator" appearing in the '075 and '330 claims. Since a definition of that phrase cannot be extracted from the claims themselves, we look to the specification¹⁴ for guidance. See McGill Inc. v. John Zink Co., 736 F.2d 666, 674, 221 USPQ 944, 949 (Fed. Cir. 1984), cert. denied, 469 U.S. 1037 (1984).

A problem now arises because there are at least four possible definitions of the phrase set forth in the specification.¹⁵ First, there is a narrow structural definition: t-PA produced through recombinant DNA technology but having the same structure as natural t-PA.¹⁶ Second, there is a broader structural definition: all products containing the "essential"¹⁷ Kringle region, and the Serine Protease region.¹⁸ Third, there is an even

¹⁴ We use the singular term because the two patents issued from applications which are divisionals of a common parent. Thus, the specifications of the two are virtually identical. All citations in this opinion are to the '075 specification.

¹⁵ Plaintiffs/appellants do not indicate which of these definitions they consider to be the appropriate one. They merely assert that the phrase should be interpreted to cover t-PA "derivatives".

¹⁶ Specification, col. 5, ll. 4 - 20:

"As used herein, "human tissue plasminogen activator" or "human t-PA" denotes human tissue extrinsic (tissue-type) plasminogen activator, produced by microbial or cell culture systems, in bioactive forms comprising a protease portion and corresponding to those tissue plasminogen activators otherwise native to human tissue. . . . It will be understood that natural allelic variations exist and occur from individual to individual. These variations may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions, substitutions, insertions, inversions or additions of (an) amino acid(s) in said sequence." (Emphasis added)

¹⁷ The specification does not define the meaning of the term "essential." Dr. Vehar testified that it means both the K1 and K2 regions. Dr. Goeddel testified that there is nothing in the patent indicating that both regions are not included in the term. Thus, we take the term to mean both regions.

¹⁸ Specification, col. 5, ll. 11 - 38:

"The potential exists . . . for the preparation of various human tissue plasminogen activator derivatives, variously modified by resultant single or multiple amino acid substitutions, deletions, additions or replacements, for example . . . Included would be the preparation of derivatives retaining the essential kringle region and serine protease region characteristic generally of the human tissue plasminogen activator described specifically herein, but otherwise modified as described above.

* * *

All such allelic variations and modifications resulting in derivatives of human tissue plasminogen activator are included within the

broader structural definition: all products containing just the enzymatically active portion, i.e., the Serine Protease portion.¹⁹ Fourth, there is a functional definition: "[I]t is capable of catalyzing the conversion of plasminogen to plasmin, binds to fibrin, and is classified as a t-PA based on immunological properties as set forth hereinabove." Col. 6, ll. 15-19.

These diverse definitions reflect either inartful drafting, a conscious attempt to create ambiguity about the scope of the claims, or a desire to claim a wide variety of materials not described or enabled in the specification. For example, it appears that some of the products contained within the third definition will not be capable of binding to fibrin because they lack the regions which have been identified as playing a role in the fibrin binding process.²⁰ Yet, the fourth definition identifies fibrin binding as an essential functional attribute of human t-PA.

An appropriate method for resolving the issue is to avoid those definitions upon which the PTO could not reasonably have relied when it issued the patent. That is an appropriate method to follow because it avoids the possibility of an applicant obtaining in court a scope of protection which encompasses subject matter that, through the conscious efforts of the applicant, the PTO did not examine.²¹ An applicant should not be able deliberately to narrow the scope of examination to avoid during prosecution scrutiny by the PTO of subject matter with the objective of more quickly obtaining a patent (or avoiding the risk of an estoppel), and then obtain in court, either literally or under the doctrine of equivalents, a scope of protection which encompasses that subject matter. See North

scope of this invention, as well as other related human extrinsic (tissue-type) plasminogen activators, similar physically and biologically, so long as the essential, characteristic human tissue plasminogen activator activity remains unaffected in kind." (Emphasis added)

¹⁹ Specification, col. 6, ll. 9 - 14:

"The tissue plasminogen activator hereof is produced containing the enzymatically active portion corresponding to native material and the term human tissue plasminogen activator defines products comprising such portion alone or together with additional amino acid sequences up to the full length molecule." (Emphasis added)

²⁰ See International Publication No. WO 89/00197, *infra* note 23, at 6, ll. 20 - 21, 26 - 27.

²¹ That seems to be the case here in view of the narrow form in which the claims are drafted, and the failure to incorporate into the claims any of the broader concepts discussed in the specification.

American Vaccine Inc., 7 F.3d at 1577, 28 USPQ2d at 1337.

[2] Under this approach, the first definition is the appropriate one to adopt because of the four, it is the most consistent with the limited form in which the claims are drafted²², and the others are hopelessly overbroad. As Dr. Goeddel testified, an infinite number of permutations of natural t-PA are covered by these other definitions. Many of these permutations would not be capable of binding to fibrin and would thus be inoperative. There is no basis provided in the specification for determining which of these permutations are operative and which are not. The point is supported by Dr. Larsen's testimony to the effect that the properties of these permutations were "totally unpredictable." Genentech acknowledged this point in two international patent applications it filed directed to the structural features which define FE1X in relation to natural t-PA.²³ The determination of which permutations are operative would thus require an undue amount of experimentation.²⁴ Thus, we are unwilling to say that the specification satisfies the enablement requirement of 35 U.S.C. § 112 ¶ 1 (1988) with respect to these broader definitions²⁵, or that the PTO

could have relied on these definitions in issuing the patent. See *In re Fisher*, 427 F.2d 833, 838-40, 166 USPQ 18, 23- 24 (CCPA 1970); see also *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied sub nom., *Genetics Inst., Inc. v. Amgen, Inc.*, 112 S.Ct. 169 (1991).

Plaintiffs argue that a protein (25E10) discussed in the specification provides a basis for interpreting the phrase "human tissue plasminogen activator" appearing in the claims broadly, on the theory that claims are to be interpreted in light of the disclosure of examples in the specification. See *SmithKline Diagnostics Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 8 USPQ2d 1468 (Fed. Cir. 1988). The difficulty with that argument is that 25E10 is not natural t-PA, and its disclosure therefore does not aid in interpreting the claims.²⁶

We conclude therefore that the phrase "human tissue plasminogen activator" appearing in the '075 and '330 claims means natural t-PA.²⁷

4. The Jury Findings Regarding the Specific Activity Limitation

Having completed our resolution of the three threshold claim interpretation questions, we consider in order the points raised by the Genetics defendants keeping in mind our standard of review: whether the jury's express or implied findings of fact are supported by substantial evidence. See *Read*, 970 F.2d at 821, 23 USPQ2d at 1431. We

²² We see no inconsistency between this conclusion and the rule that the PTO should give claims their broadest reasonable interpretation during prosecution. See *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550 (CCPA 1969). The operative word is *reasonable*: the PTO has no such obligation regarding *unreasonable* interpretations.

²³ Genentech characterized the effects of the amino acid substitution at position 117 of the K1 region as "unexpected." European Patent Application Publication No. 0 238 304, entitled "MODIFIED HUMAN TISSUE-TYPE PLASMINOGEN ACTIVATOR AND ITS PREPARATION," filed by Genentech on March 17, 1987 and published September 23, 1987, at 2, II, 55 - 59. It likewise characterized the effects of the deletion of the F and E regions as "surprising and unexpected." International Publication No. WO 89/00197, entitled "IMPROVED PROCESSES FOR THE TREATMENT OF VASCULAR DISEASE," filed by Genentech on June 27, 1988 and published January 12, 1989, at 16, II, 32 - 33.

²⁴ The point is supported by unrebutted testimony to the effect that the Genetics defendants expended a significant amount of effort — \$20 million and 130 man-years — to develop FE1X notwithstanding the prior work that led to the filing of the '075 and '330 patents.

²⁵ There may also be a problem with satisfaction of the definiteness and description requirements of 35 U.S.C. §112 in relation to these other definitions, especially the fourth functional definition. The DNA isolate which is the subject of the '075 and '330 claims is itself defined in

functional terms, i.e., as any sequence that encodes human t-PA. A conclusion that the phrase "human tissue plasminogen activator" is also defined in functional terms would give rise to a definiteness problem because a competitor could not then reasonably determine what DNA sequences are within the scope of the claims and which are not. It would also give rise to a problem with the description requirement because the specification does not even remotely describe all the DNA sequences that encode the proteins within the scope of the functional definition. See *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

²⁶ The record establishes that 25E10 differs in significant characteristics from natural t-PA, the inventors' testimony to the contrary notwithstanding.

²⁷ It is undisputed that FE1X is not a naturally occurring variant of the full-length sequence of human t-PA. Thus, unlike the district court, we do not reach the issue of whether the phrase "human tissue plasminogen activator" as it appears in the claims includes within its scope naturally-occurring variants of the full-length sequence.

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begin with the question of whether the jury's implied conclusion — that the specific activity limitation appearing in the '603 claims was met by FE1X either literally or equivalently — is supported by substantial evidence.¹¹ We conclude that it is not.

As we have said, "substantial evidence is more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Biodes Corp. v. Loredan Biomedical Inc.*, 946 F.2d 850, 859, 20 USPQ2d 1252, 1259 (Fed. Cir. 1991), cert. denied, 112 S.Ct. 2957 (1992) (quoting *Consolidated Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)). Plaintiffs point to the following three pieces of evidence: (1) Dr. Larsen's testimony that the specific activity of FE1X is in the range from 350,000 to 450,000 IU/mg., (2) statements in an internal Institute document to the effect that the specific activity of FE1X is "similar" to that of natural t-PA¹², and (3) a publication co-authored by Dr. Collen stating that the specific activity of FE1X is 440,000 IU/mg.¹³

To begin with, the specific activity measurements reported by Dr. Larsen were made using the chromogenic substrate assay, and there is no evidence that measurements made using this assay are comparable to those made using the bovine fibrin plate assay. In fact, all the evidence of record addressing this subject indicates that the two methods are not comparable. Dr. Larsen's testimony on this point is representative:

A Excuse me, I believe [the chromogenic assay measurements] requires a clarification. You're really talking about two totally different assays.

Q I understand that.

A So it's apples and oranges. You cannot compare the two numbers

Q I understand. And at your deposition when you were asked about the specific activity for FE1X was measured against the international t-PA, you said it ranged

¹¹ The jury was properly instructed that to find infringement under the doctrine of equivalents, they had to find that each limitation of the claim was met by the accused product either literally or by an equivalent. See *Corning Glass Works v. Sumitomo Electric USA Inc.*, 868 F.2d 1251, 1259, 9 USPQ2d 1962, 1968 (Fed. Cir. 1989).

¹² Second Generation t-PA: A report on the tissue plasminogen activator program at Genetics Institute, September 26, 1988.

¹³ Désiré Collen et al., Pharmacokinetics and Thrombolytic Properties of Deletion Mutants of Human Tissue-Type Plasminogen Activator in Rabbits, 71 Blood 216, 218 (1988).

from 350,000 to 450,000 IU's per milligram?

A Using a chromogenic substrate assay, and not the fibrin plate assay which appears to be the standard for measuring plasminogen activator activity with respect to these patent disputes. So it is completely distinct from anything that appears to be relevant to me in this trial.

Plaintiffs assert that a publication co-authored by Dr. Larsen shows that results obtained using the chromogenic assay are comparable to those obtained using the bovine assay.¹¹ We cannot agree. Although that document presents results obtained using the two methods, it hardly establishes that the two methods are comparable. In fact, it implies just the opposite. The two figures reported for FE1X are very different: 334 ± 45 units/μg. for the chromogenic assay, and 440 units/μg. for the bovine fibrin plate assay.

Likewise, the statements in the internal Institute report do not provide the necessary support. First, they are qualitative whereas the necessary comparison is quantitative. Second, they are based on a synthetic assay which, unlike the bovine fibrin plate assay, does not measure the ability to dissolve clots.

Finally, the 440,000 figure reported in the publication co-authored by Dr. Collen was measured from material prepared by Leuven; it is not clear what relationship that material bears to the accused product that is the subject of this lawsuit. Dr. Collen's testimony on this precise point was equivocal. When asked whether this material was the same substance as the accused product, he merely said the "description" was the same. Moreover, other measurements reported in that publication and taken in the same manner fall outside the range of permissible scientific error and thus bring into question all the measurements reported.¹²

The only evidence in the record which is

¹¹ Linda Hansen et al., Functional Effects of Asparagine-linked Oligosaccharide on Natural and Variants Human Tissue-type Plasminogen Activator, 263 J. Biological Chemistry 15713, 15715 (1988).

¹² For example, a value of 640,000 IU/mg. is reported for the specific activity of native t-PA. But Dr. Collen testified that the "consensus attitude" of those who work in the area is that, if an assay is performed "properly and carefully", the resulting measurement for native t-PA should be 500,000 plus or minus 25%, i.e., between 375,000 and 625,000, and that a value above that range was not achievable in nature. The implication is that the reported figures, including the 440,000 figure, were all biased upwards due to the presence of an unknown factor which affected all.

probative on the question of the specific activity of FE1X is the testimony of plaintiffs' expert Dr. Mann. According to that testimony, the specific activity of FE1X using the bovine fibrin plate assay is 253,800 IU/mg. plus or minus 18%, i.e., 208,116 to 299,484. That is significantly closer to the prior art value of 266,000 than it is to the claimed range¹³, and may even be less than that value¹⁴. FE1X is thus outside the permissible range of equivalents through the application of prosecution history estoppel.¹⁵ No reasonable jury could have concluded otherwise. The trial court thus erred in denying the Genetics defendants' motions for JMOL in relation to the '603 patent under the doctrine of equivalents.

5. The Jury Findings Regarding the Human Tissue Plasminogen Activator Limitation

We next consider whether there is evidence in the record sufficient to support the jury's implied conclusion that the "human tissue plasminogen activator" limitation appearing in the '075 and '330 claims is met by FE1X.¹⁶ FE1X does not literally meet the limitation — it is not natural t-PA. Thus, the question is whether the evidence supports a finding that this limitation is met by an equivalent element of FE1X under the doctrine of equivalents.

To support such a finding, the evidence must be sufficiently particularized to meet the three prong test of equivalency enunciated in *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608, reh'g denied, 340 U.S. 845 (1950) requiring a showing of substantial identity of function, way, and result. *Malta*, 952 F.2d at 1327, 21

¹³ The upper limit of the testified-to range, 299,484, is significantly closer to the prior art value of 266,000 than it is to the lower limit of "about 500,000", i.e. 375,000, as determined in accordance with Dr. Collen's testimony. As Dr. Mann put it, the difference between the specific activity of FE1X and the claimed range is "outside the range of quibbles."

¹⁴ The mean value of the testified-to range, 253,800, is less than the prior art value of 266,000.

¹⁵ Prosecution history estoppel is a question of law, which we are free to analyze on appeal without deference to any implied finding of the jury on this issue. See *Hoganas AB v. Dresser Indus. Inc.*, 9 F.3d 948, 952, 28 USPQ2d 1936, 1939 (Fed. Cir. 1993).

¹⁶ In view of our conclusion regarding the specific activity limitation in the '603 claims, we do not need to determine whether there is substantial evidence in the record to support the jury's implied conclusion that FE1X met the "human plasminogen activator" limitation appearing in the '603 claims.

USPQ2d at 1166; *Lear Siegler Inc. v. Sealy Mattress Co.*, 873 F.2d 1422, 1425-26, 10 USPQ2d 1767, 1770 (Fed. Cir. 1989). If any one of the prongs is unsupported, the finding of equivalency cannot stand.

At the outset, we are confronted with a problem: The issue of whether the 'way' or 'result' prongs are met is highly dependent upon how broadly one defines the 'function' of human t-PA. If, as the trial court thought, a broad definition is appropriate — stimulating "the dissolution of fibrin clots through the cleavage of plasminogen to plasmin"¹⁷ — then it is difficult to imagine how FE1X, or any version of t-PA for that matter, would avoid infringement under the doctrine of equivalents because t-PA, or any operative variant, would by definition necessarily perform this function in the same general way with the same general results. However, if the definition of t-PA set forth in the specification is adopted — catalyzing the conversion of plasminogen to plasmin, [and] bind[ing] to fibrin¹⁸ — then the equivalence question becomes a much closer one.

[3] The operative definition for purposes of equivalency analysis is the intended function as seen in the context of the patent, the prosecution history, and the prior art. *Graver Tank*, 339 U.S. at 609; *Zenith Lab. Inc. v. Bristol-Myers Squibb Co.*, ____ F.3d ____, ____ 30 USPQ2d 1285, 1291 (Fed. Cir. 1994). Based on our review of these materials, we conclude that no reasonable jury could have adopted the broad definition suggested by the trial court. As noted, the specification expressly defines fibrin binding as a critical component of the "function" of human t-PA. Col. 6, ll. 16-19. Other evidence confirms this. According to a British patent application filed by Foundation, it is critical in a therapeutic sense — it reduces the risk of hemorrhaging.¹⁹ Moreover, as Drs. Goeddel and Collen testified, the fibrin binding affinity of human t-PA is a critical distinction between this protein and the two prior plasminogen activators, urokinase and streptokinase. Thus, a functional definition of t-PA which ignores this distinction would result in a range of equivalents which impermissably reads on the

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prior art.²⁰ See *USPQ2d at 1166*

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¹⁹ 14 USPQ2d at 1370.

²⁰ Col. 6, ll. 16 - 19.

²¹ U.K. Patent Application Publication No. 2 176 703 A, entitled "TISSUE PLASMINOGEN ACTIVATOR," filed by Foundation on May 27, 1986 and published January 7, 1987, at 1, ll. 43 - 55.

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USPQ2d at 1291 n.9.

We conclude that the "function" of hu-
man t-PA for purposes of the equivalency
analysis includes fibrin binding, and no rea-
sonable jury could have concluded otherwise.
In light of this definition, we find that the
record is devoid of any particularized evi-
dence or linking argument showing that
FE1X functions in substantially the same
way as human t-PA or achieves substantially
the same results.¹¹

Plaintiffs point to the testimony of several
witnesses to the effect that the Kringle 2
(K2) region of amino acids is present in both
FE1X and human t-PA, and that this region
plays a role in the ability of both to bind to
fibrin. Dr. Larsen testified:

Q And FE1X binds the fibrin, doesn't it?

A Weakly.

Q But it binds the fibrin?

A Weakly.

Q Weakly. And it binds the fibrin through
the second kringle region, doesn't it?

A I don't know.

Q You don't know how it binds the fibrin?

A I mean that is speculation in the litera-
ture, but there are conflicting reports to
that point.

Q But there are literature reports that
suggest that the finger region is involved in
the binding to fibrin, as well as the kringle
two region; isn't that correct?

A That is what is generally believed, yes.

Q And natural t-PA also binds to fibrin
through kringle two, doesn't it?

A Assuming that its kringle two, yes.

Dr. Wetlauser testified:

Q Does GI's FE1X bind to fibrin?

A GI's bind to fibrin? I think it does, but
in a weaker way than the full-length
material.

¹⁰ The jury was properly instructed that the scope of equivalents imparted to a claim cannot be so broad as to cover that which the prior art discloses. See *Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677, 684, 14 USPQ2d 1942, 1948 (Fed. Cir.), cert. denied, 111 S.Ct. 537 (1990).

¹¹ Another problem faced by plaintiffs/appellees is that the doctrine of equivalents is not available for the attainment in court of a scope of protection which encompasses subject matter deliberately removed from examination by the PTO during prosecution through narrow claiming. This is a reflection of the rule enunciated in *Perkin-Elmer Corp. v. Westinghouse Electric Corp.*, 822 F.2d 1528, 3 USPQ2d 1321 (Fed. Cir. 1987) that it is impermissible to erode under the doctrine of equivalents "meaningful limitations of the claim on which the public is entitled to rely in avoiding infringement." *Id.* at 1532, 3 USPQ2d at 1324.

Q Binds in a weaker way?

A Yes.

Q In your view, does it bind to fibrin in a
completely different way than the full-
length human t-PA?

A No. Clearly there are common elements
in the binding of the two t-PA's.

Dr. Larsen's testimony is speculative, and
Dr. Wetlauser's testimony is tentative and
conclusory. Even assuming that the K2 re-
gion does play a role in the binding function
of both, that hardly establishes that the two
bind to fibrin in substantially the same way
with substantially the same results, partic-
ularly in view of the overwhelming and undis-
puted evidence that the two possess dramati-
cally different properties and structure.

First, there is the undisputed testimony of
Drs. Collen and Larsen that the fibrin bind-
ing affinity of FE1X is less than half, i.e.,
about 40%, of that of human t-PA as a
consequence of the deletion of the E and F
regions in FE1X.

Second, there is undisputed evidence
showing that the amino acid substitution at
position 117 of the K1 region eliminates a
glycosylation site, and thus prevents a carbo-
hydrate side chain from being attached to
the protein during post-translational modifi-
cations by the host mammalian cell. Accord-
ing to Dr. Larsen, the deletion of the F and E
regions standing alone would result in a
protein that would be therapeutically inef-
fective in that it would be incapable of bind-
ing to fibrin at all; preventing the attachment
of the carbohydrate side chain increases the
binding affinity of FE1X sufficiently to
make it therapeutically effective. Thus, the
mode of binding is hardly substantially the
same.

Third, there is the undisputed evidence
that FE1X behaves significantly differently
than human t-PA in the human body. It has
a half-life¹² about ten times that of natural
t-PA and it has a significantly decreased
affinity for binding to endothelial cells¹³ in
relation to human t-PA. Genentech acknowl-

¹² The "half-life" is a measurement of the length of time a dosage is retained in the human body. According to Dr. Marder's and Dr. Col-
len's testimony, the long half-life of FE1X in relation to human t-PA — about 40 minutes for FE1X versus about 4 minutes for human t-PA — is a significant advantage because it avoids the need for continuous administration over a pro-
longed period in order to remove a clot.

¹³ "Endothelial" cells are the cells that make up the lining of blood vessels. The reduced bind-
ing affinity to endothelial cells is likewise a sig-
nificant advantage because it reduces the risk of uncontrolled bleeding that is present with the
administration of human t-PA.

edged the significance of these advantages in the two international patent applications noted earlier in this opinion.⁴⁴ Thus, the results achieved are hardly substantially the same.

We are mindful that the state of the science in this area of endeavor is very imprecise.⁴⁵ Thus, it would be inappropriate to interpret *Malta* as requiring plaintiffs/appellees to prove the specific mechanism by which FE1X binds to fibrin, or to prove that the different properties and structure exhibited by FE1X bear no relation to the binding function. Our only point is that the showing that the K2 region plays a role in the binding function of each is insufficient, particularly in view of the profound differences in the properties and structure possessed by each.

For all the foregoing reasons, we conclude the trial court erred in denying the Genetics defendants' motion for JMOL in relation to the '075 and '330 patents under the doctrine of equivalents.⁴⁶

SUMMARY

The trial judge should have granted JMOL in favor of the Genetics defendants on the doctrine of equivalents findings by the jury because:

1. The specific activity limitation appearing in the '603 claims means specific activity as measured using the bovine fibrin plate assay.

2. Considering the '603 prosecution history, the specific activity of FE1X does not as a matter of law meet the specific activity limitation appearing in the '603 claims under the doctrine of equivalents.

3. The human tissue plasminogen activator limitation appearing in the '075 and '330

claims means natural t-PA. The jury's implied conclusion that FE1X meets the human tissue plasminogen activator limitation appearing in the '075 and '330 claims under the doctrine of equivalents is not supported by substantial evidence.

CONCLUSION

For all the foregoing reasons, we reverse.⁴⁷
REVERSED

Lourie, J., concurring.

I join the opinion of the majority, but I would adopt a different means to interpret the expression "human tissue plasminogen activator" (t-PA). Moreover, I wish to point out an additional reason why I believe that the accused FE1X cannot infringe a claim to t-PA under the doctrine of equivalents.

The independent claims at issue in the '075 and '330 recombinant patents contain no definition for the DNA isolate other than that it encodes human t-PA. Such a claim, defining a substance only by its function, encompassing all substances that accomplish that result, is akin to a single means claim, which might fail to satisfy the definiteness requirement of 35 U.S.C. § 112. See *Fiers v. Sugano*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Such a claim avoids that problem only when the term "human tissue plasminogen activator" has definitive meaning, when it describes a specific compound. That term is in fact definite, as it is well established that human t-PA is a protein consisting of 527 amino acids. Thus, all the claims which depend upon a definition of human t-PA are limited to that specific compound and any other compounds considered under law as equivalent thereto.⁴⁸ The trial court, of course, held that there was no literal infringement.

Under the doctrine of equivalents, an accused compound can be held to infringe if, *inter alia*, it represents only an insubstantial change from the claimed compound. See *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607, 610 (1950). The

⁴⁴ See International Publication No. WO 89/00197, *supra* note 23, at 2, ll. 29 - 31; EPO Publication No. 0 238 304, *supra* note 23, at 2, ll. 55 - 59.

"As Genentech put it: "[T]here has been much confusion and uncertainty surrounding the functional significance of the various structural domains . . ." International Publication No. WO 89/00197, *supra* note 23, at 16, ll. 20 - 22.

"In view of our disposition of the doctrine of equivalents question on the basis of the function-/way/result test, we need not reach the alternative basis for resolving that question discussed in the concurrence. Such a discussion is also premature given the pendency of *Hilton Davis Chemical Co. v. Warner-Jenkinson Company, Inc.*, No. 93-1088 (Fed. Cir. ordered *en banc* Dec. 3, 1993 and argued *en banc* Mar. 3, 1994), in which the issue of whether factors other than the function-/way/result factors are relevant to the doctrine of equivalents question is to be resolved by the full court.

⁴⁵ In view of our disposition of this appeal, we need not reach the points made by the Genetics defendants relating to a new trial, or the binding effect of the judgment in relation to GI Manufacturing. We only observe that, as we have discussed, the trial court erred in undertaking the task of claim construction and then failing to instruct the jury on the proper claim construction it was to apply. While that would be sufficient grounds to remand for a new trial, in view of our disposition of this appeal, no remand is warranted.

⁴⁶ Senior Circuit Judge Cowen agrees with this analysis.

accused compound that contains fewer than the This is not a substantial on the half-life of ed in the claim accused FE1X independently quiring an es costing \$20 m meaning, as a cannot be held

Thus, this c results not onl the claims for fact-finder unti, way, res 339 U.S. at analysis fail to cially when th cal, as it is t part of the "w "result"? Is t as stated by t "way" t-PA d illustrate the way, result t substance wo than what it define. The o properly cons have led to a sity of the diffe claimed comp development, lead to a conc

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JUDICIAL PROCEDUR

1. Procedure

Special ve ment action. ity, infringem and which w complexity c propriate, and t authorized to relevant to c Civ.P. 49(a) upon those Civ.P. 58.

The jury's interpretation meets the limitation 330 claims under 35 U.S.C. § 101. The claim is not supported by evidence.

ons, we reverse.⁴⁷

majority, but I mean to interpret sue plasminogen. I wish to point out why I believe that infringe a claim to equivalents.

at issue in the patents contain solute other than t-PA. Such a claim, by its function, is that accomplish single means claim, the definiteness 112. See *Fiers v. Boehringer Ingelheim*, 71, 25 USPQ2d 112. Such a claim when the term "inventor" has describes a species in fact definite, human t-PA is a protein consisting of amino acids. Thus, upon a definition to that specific compounds considered thereto. The court held that there was no

equivalents, an action could be brought to infringe if, by an insubstantial compound. See *Linde Air Prods.*, 610 (1950). The

of this appeal, we made by the Genetics Institute, or the binding of GI to GI. As we have done in undertaking the trial, and then failing to claim construction would be sufficient trial in view of our remand is in agreement with this

accused compound in this case consists of a protein that contains 446 amino acids, 15% fewer than the t-PA referred to in the claims. This is not an insubstantial change, but a substantial one. Moreover, it has ten times the half-life of natural t-PA. The t-PA recited in the claims was not copied, since the accused FEIIX is a very different material, independently invented and developed, requiring an estimated 130 man-years, and costing \$20 million. If claims are to have any meaning, as a matter of law such a substance cannot be held to be infringing.

Thus, this case illustrates the problem that results not only when a court fails to construe the claims for the jury, but also when the fact-finder unduly focuses only on the function, way, result analysis of *Graver Tank*, 339 U.S. at 608. These limited means of analysis fail to fully elucidate the issue, especially when the patented material is a chemical, as it is here. Is the increased half-life part of the "way" analysis or is it a different "result"? Is the binding to fibrin "function," as stated by the majority, or is it part of the "way" t-PA dissolves clots? These questions illustrate the shortcomings of the function, way, result tests which relate to "how" a substance works, i.e., what it does, rather than what it is, which claims purport to define. The other aspects of *Graver Tank*, if properly considered by the fact-finder, would have led to a sounder result. The substantiality of the difference between the accused and claimed compounds, the fact of independent development, and the lack of copying, all lead to a conclusion of lack of infringement.

U.S. District Court Western District of Wisconsin

Oscar Mayer Foods Corp. v. Conagra Inc.

No. 92-C-718-S

Decided February 24, 1994

JUDICIAL PRACTICE AND PROCEDURE

1. Procedure — Jury trials (§410.42)

Special verdict form, in patent infringement action, which isolated issues of validity, infringement, willfulness, and damages, and which was consistent with nature and complexity of issues presented, was appropriate, and thus federal district court is not authorized to make de novo findings of fact relevant to obviousness pursuant to Fed.R.Civ.P. 49(a) and to enter judgment based upon those findings pursuant to Fed.R.Civ.P. 58.

PATENTS

2. Patentability / Validity — Obviousness — Relevant prior art — Particular inventions (§115.0903.03)

Substantial evidence supports jury's verdict that claimed process of adding sodium lactate to precooked, anaerobically packaged poultry or fish was not obvious, even though it was known that sodium lactate had certain preservative properties, since extent to which sodium lactate controlled growth of bacteria was unexpected in view of prior art.

REMEDIES

3. Monetary — Damages — Patents — Lost profits (§510.0507.05)

Jury's award of \$9.25 million lost profits to patent infringement plaintiff was consistent with conflicting evidence, and was based upon jury instructions which properly specified that plaintiff which admits presence of acceptable non-infringing substitutes may nevertheless recover lost profits if it proves instead its probable market share of infringing sales.

4. Monetary — Damages — Patents — Lost profits (§510.0507.05)

Patent infringement plaintiff's decision to exclusively license its patent under contract that provided for sublicenses did not thereby preclude it from recovering damages for lost profits from infringers which chose not to accept sublicense offered by plaintiff's licensee.

5. Monetary — Damages — Patents — Increased damages (§510.0507.07)

Monetary — Attorney's fees; costs — Patents — Exceptional case (§510.0905.03)

Award of increased damages in patent infringement action is not warranted pursuant to 35 USC 284, despite defendants' willful unlicensed use of plaintiff's patented process, in view of strength of defendants' invalidity defense, since award of enhanced damages would be inappropriate under such circumstances, given public interest in legitimate challenges to validity of patent monopoly; similarly, award of attorney's fees is not warranted pursuant to 35 USC 285.

6. Monetary — Damages — Prejudgment interest (§510.0511)

Award of prejudgment interest is warranted in order to fully compensate patent infringement plaintiff, and in view of lack of any special circumstances, such as delay by plaintiff in commencing lawsuit.

and instead render our decision on the merits. Fed. R. App. P. 42(b). The judgment below is affirmed.

Court of Appeals, Federal Circuit

In re Bell
No. 92-1375
Decided April 20, 1993

PATENTS

1. Patentability/Validity — Obviousness — In general (§115.0901)

Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§115.0903.03)

Established relationship in genetic code between nucleic acid and protein it encodes does not make gene *prima facie* obvious over its correspondent protein in same way that closely related homologs, analogs, and isomers in chemistry may create *prima facie* case, since there are vast number of nucleotide sequences that might code for specific protein due to "degeneracy" of genetic code; gene might be obvious over correspondent protein if latter is known amino acid sequence specified exclusively by "unique" codons, but claims in application for nucleic acid molecules containing human sequences coding for human insulin-like growth factors I and II (IGF) are not obvious in view of cited prior art disclosing amino acid sequences for IGF I and II, since cited art suggests nearly infinite number of sequences, but fails to suggest which of those are human nucleic acid sequences coding for IGF.

2. Patentability/Validity — Obviousness — Combining references (§115.0905)

Reference disclosing general method for isolating genes, in combination with prior art disclosing amino acid sequences for insulin-like growth factors I and II (IGF), does not render obvious application claims for nucleic acid molecules containing human sequences coding for human IGF I and II, since, absent some teaching or suggestion supporting combination, obviousness is not established by combining teachings of prior art to produce claimed invention, since reference in question teaches away from invention claimed in application by emphasizing importance of "unique" codons, and since reference thus cannot be held to "fairly suggest"

that its teachings be combined with those of prior art, which discloses amino acid sequences lacking "unique" codons.

3. Patentability/Validity — Obviousness — In general (§115.0901)

Patent construction — Claims — Process (§125.1309)

Similarities between method by which applicants made claimed nucleic acid molecules, and method for isolating genes taught by prior art reference, do not render application claims obvious, since applicants claim compositions, rather than method of making them.

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Graeme I. Bell, Leslie B. Rall and James P. Merryweather, serial no. 07/065,673 ("preproinsulin-like growth factors I and II"). From decision affirming examiner's final rejection of claims 25-46, applicants appeal. Reversed.

Robert P. Blackburn, Emeryville, Calif. (Debra A. Shetka and Thomas E. Ciotti, of Morrison & Foerster, Palo Alto, Calif., and Donald S. Chisum, of Morrison & Foerster, Seattle, Wash., on brief), for appellant.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor, on brief; John W. Dewhurst, Lee E. Barrett, Richard E. Schafer, and Albin F. Drost, of counsel), for PTO.

Before Rich, Lourie, and Schall, circuit judges.

Lourie, J.

Applicants Graeme I. Bell, Leslie B. Rall, and James P. Merryweather (Bell) appeal from the March 10, 1992 decision of the U.S. Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences, Appeal No. 91-1124, affirming the examiner's final rejection of claims 25-46 of application Serial No. 065,673, entitled "Preproinsulin-Like Growth Factors I and II," as unpatentable on the ground of obviousness under 35 U.S.C. § 103 (1988). Because the Board erred in concluding that the claimed nucleic acid molecules would have been obvious in light of the cited prior art, we reverse.

BACKGROUND

The claims of the application at issue are directed to nucleic acid molecules (DNA and

RNA)' containing human sequences² which code for human insulin-like growth factors I and II (IGF), single chain serum proteins that play a role in the mediation of somatic cell growth following the administration of growth hormones.³

The relevant prior art consists of two publications by Rinderknecht⁴ disclosing amino acid sequences for IGF-I and -II and U.S. Patent 4,394,443 to Weissman et al., entitled

² A basic familiarity with recombinant DNA technology is presumed. For a general discussion, see *In re O'Farrell*, 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988).

³ Interchangeably referred to as "native" sequences and "genes."

⁴ Claim 25 is conceded to be representative of the claims at issue:

A composition comprising nucleic acid molecules containing a human sequence encoding insulin-like growth factor (hIGF) substantially free of nucleic acid molecules not containing said hIGF sequence, wherein said hIGF sequence is selected from the group consisting of:

(a) 5'-GGA CCG GAG ACG CUC UGC GGG GCU GAG CUG GUG GAU GCU CUU CAG UUC GUG UGU GGA GAC AGG GGC UUU UAU UUC AAC AAG CCC ACA GGG UAU GGC UCC AGC AGU CGG AGG GCG CCU CAG ACA GGU AUC GUG GAU GAG UGC UGC UUC CGG AGC UGU GAU CUA AGG AGG CUG GAG AUG UAU UGC GCA CCC CUC AAG CCU GCC AAG UCA GCU-3', wherein U can also be T;

(b) 5'-GCU UAC CGC CCC AGU GAG ACC CUG UGC GGC GGG GAG CUG GUG GAC ACC CUC CAG UUC GUC UGU GGG GAC CGC GGC UUC UAC UUC AGC AGG CCC GCA AGC CGU GUG AGC CGU CGC AGC CGU GGC AUC GUU GAG GAG UGC UGU UUC CGC AGC UGU GAC CUG GCC CUC CUG GAG ACG UAC UGU GCU ACC CCC GCC AAG UCC GAG-3', wherein U can also be T;

(c) nucleic acid sequences complementary to (a) or (b); and

(d) fragments of (a), (b) or (c) that are at least 18 bases in length and which will selectively hybridize to human genomic DNA encoding hIGF.

The other rejected claims are apparently directed to cellular hosts transformed with the claimed nucleic acid sequences. Because their fate is dependent upon that of claim 25, neither appellant nor the Patent and Trademark Office have considered them separately and we will not do so either.

Rinderknecht et al., *The Amino Acid Sequence of Human Insulin-like Growth Factor I and Its Structural Homology with Proinsulin*, 253 *The Journal of Biological Chemistry* 2769-76 (1978); Rinderknecht et al., *Primary Structure of Human Insulin-like Growth Factor II*, 89 *FEB Letters* 283-86 (May 1978).

"Method for Cloning Genes." Weissman describes a general method for isolating a gene for which at least a short amino acid sequence of the encoded protein is known. The method involves preparing a nucleotide probe corresponding to the known amino acid sequence and using that probe to isolate the gene of interest. It teaches that it is advantageous to design a probe based on amino acids specified by unique codons.⁵ The Weissman patent specifically describes the isolation of a gene which codes for human histocompatibility antigen, a protein unrelated to IGF. It describes the design of the probe employed, stating that it was based on amino acids specified by unique codons.

The examiner rejected the claims as obvious over the combined teachings of Rinderknecht and Weissman. She determined that it would have been obvious, "albeit tedious," from the teachings of Weissman to prepare probes based on the Rinderknecht amino acid sequences to obtain the claimed nucleic acid molecules. According to the examiner, "it is clear from [Weissman] that the ordinary artisan knows how to find the nucleic acid when the amino acid sequence is known" and that "the claimed sequences and hosts would have been readily determinable by and obvious to those of ordinary skill in the art at the time the invention was made."

The Board affirmed the examiner's rejection, holding that the examiner had established a *prima facie* case of obviousness for the claimed sequences "despite the lack of conventional indicia of obviousness, e.g., structural similarity between the DNA which codes for IGF-I and the amino acid sequence of the polypeptide which constitutes [sic] IGF-I." Slip op. at 6. The Board reasoned that "although a protein and its DNA are not structurally similar, they are correspondently linked via the genetic code." *Id.* at 4 n.1. In view of Weissman, the Board concluded that there was no evidence "that one skilled in the art, knowing the amino acid sequences of the desired proteins, would not have been able to predictably clone the de-

sired DNA sequence." *Id.* a

The issue before correctly determines the sequence of a preference indicated cloning renders obvious.

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We review an by the Board de n 488, 493, 20 USP 1991). Bell argu shown how the f alone or in combi claimed invention to establish a obviousness.

We agree. The establishing a ca ness. *In re Fine*, USPQ2d 1596, 1 prima facie case c when the teachin would appear to t subject matter to the art." *In re* 1051, 189 USPQ

The Board sup that the "corre gene and its ence code renders the no acid sequence amounts to a reje necht references clusion is the pro related homolog chemistry may cr *In re Dillon*, 919 1897, 1904 (Fed. denied, 111 S. C lished relationshi between a nucleic codes also makes over its correspo

[1] We do not may be true tha the protein, one hypothesize poss sponding gene a potential for obt because of the code, there are a sequences that protein. In the c without contradi amino acid sequ more than 10

⁵ A sequence of three nucleotides, called a codon, codes for each of the twenty natural amino acids. Since there are twenty amino acids and sixty-four possible codons, most amino acids are specified by more than one codon. This is referred to as "degeneracy" in the genetic code. The term "unique" refers to an amino acid coded for by a single codon. See *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08 n.4, 18 USPQ2d 1016, 1022 n.4 (Fed. Cir.), cert. denied, 112 S. Ct. 169 (1991).

sired DNA sequences without undue experimentation." *Id.* at 8.

The issue before us is whether the Board correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning renders the gene *prima facie* obvious.

DISCUSSION

We review an obviousness determination by the Board *de novo*. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Bell argues that the PTO has not shown how the prior art references, either alone or in combination, teach or suggest the claimed invention, and thus that it has failed to establish a *prima facie* case of obviousness.

We agree. The PTO bears the burden of establishing a case of *prima facie* obviousness. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." *In re Rinehart*, 531 F.2d 1048, '051, 189 USPQ 143, 147 (CCPA 1976).

The Board supported the examiner's view that the "correspondent link" between a gene and its encoded protein via the genetic code renders the gene obvious when the amino acid sequence is known. In effect, this amounts to a rejection based on the Rinderknecht references alone. Implicit in that conclusion is the proposition that, just as closely related homologs, analogs, and isomers in chemistry may create a *prima facie* case, see *In re Dillon*, 919 F.2d 688, 696, 16 USPQ2d 1897, 1904 (Fed. Cir. 1990) (*in banc*), cert. denied, 111 S. Ct. 1682 (1991), the established relationship in the genetic code between a nucleic acid and the protein it encodes also makes a gene *prima facie* obvious over its correspondent protein.

[1] We do not accept this proposition. It may be true that, knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. In the case of IGF, Bell has argued without contradiction that the Rinderknecht amino acid sequences could be coded for by more than 10^{10} different nucleotide se-

quences, only a few of which are the human sequences that Bell now claims. Therefore, given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious.

Bell does not claim all of the 10^{10} nucleic acids that might potentially code for IGF. Neither does Bell claim all nucleic acids coding for a protein having the biological activity of IGF. Rather, Bell claims only the human nucleic acid sequences coding for IGF. Absent anything in the cited prior art suggesting which of the 10^{10} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.

This is not to say that a gene is never rendered obvious when the amino acid sequence of its coded protein is known. Bell concedes that in a case in which a known amino acid sequence is specified exclusively by unique codons, the gene might have been obvious. Such a case is not before us.¹ Here, where Rinderknecht suggests a vast number of possible nucleic acid sequences, we conclude that the claimed human sequences would not have been obvious.

[2] Combining Rinderknecht with Weissman does not fill the gap. Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *In re Fine*, 837 F.2d at 1075, 5 USPQ2d at 1598 (citing *ACS Hosp. Sys. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). What a reference teaches and whether it teaches toward or away from the claimed invention are questions of fact. See *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960-61, 220 USPQ 592, 599-600 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 [225 USPQ 232] (1984).

While Weissman discloses a general method for isolating genes, he appears to teach away from the claimed invention by emphasizing the importance of unique codons for the amino acids. Weissman suggests that it is generally advantageous to design a probe based on an amino acid sequence specified by unique codons, and also teaches that it is "counterproductive" to use a primer having

¹ We also express no opinion concerning the reverse proposition, that knowledge of the structure of a DNA, e.g., a cDNA, might make a coded protein obvious.

more than 14-16 nucleotides unless the known amino acid sequence has 4-5 amino acids coded for by unique codons. Bell, in contrast, used a probe having 23 nucleotides based on a sequence of eight amino acids, none of which were unique. Weissman therefore tends to teach away from the claimed sequences since Rinderknecht shows that IGF-I has only a single amino acid with a unique codon and IGF-II has none.

The PTO, in urging us to affirm the Board, points to the suggestion in Weissman that the disclosed method can "easily" be applied to isolate genes for an array of proteins including peptide hormones. The PTO thus argues that in view of Weissman, a gene is rendered obvious once the amino acid sequence of its translated protein is known. We decline to afford that broad a scope to the teachings of Weissman. While "a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests," *In re Burckel*, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979), we cannot say that Weissman "fairly suggests" that its teachings should be combined with those of Rinderknecht, since it nowhere suggests how to apply its teachings to amino acid sequences without unique codons.

We conclude that the Board clearly erred in determining that Weissman teaches toward, rather than away from, the claimed sequences. Therefore, the requisite teaching or suggestion to combine the teachings of the cited prior art references is absent, *see In re Fine*, 837 F.2d 1075, 5 USPQ2d at 1599, and the PTO has not established that the claimed sequences would have been obvious over the combination of Rinderknecht and Weissman.

[3] Finally, the PTO emphasizes the similarities between the method by which Bell made the claimed sequences and the method taught by Weissman. The PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made. *See In re Thorpe*, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985) ("The patentability of a product does not depend on its method of production.").

CONCLUSION

Because we conclude that the combination of prior art references does not render the claimed invention obvious, we reverse the

Board's decision affirming the examiner's rejection of claims 25-46.
REVERSED

Court of Appeals, Fifth Circuit

Matrix Essentials Inc. v. Emporium Drug Mart Inc. of Lafayette

No. 91-4457

Decided April 19, 1993

TRADEMARKS AND UNFAIR TRADE PRACTICES

1. Infringement; conflicts between marks — Likelihood of confusion — In general (§350.0301)

Infringement; conflicts between marks — Passing off (§350.07)

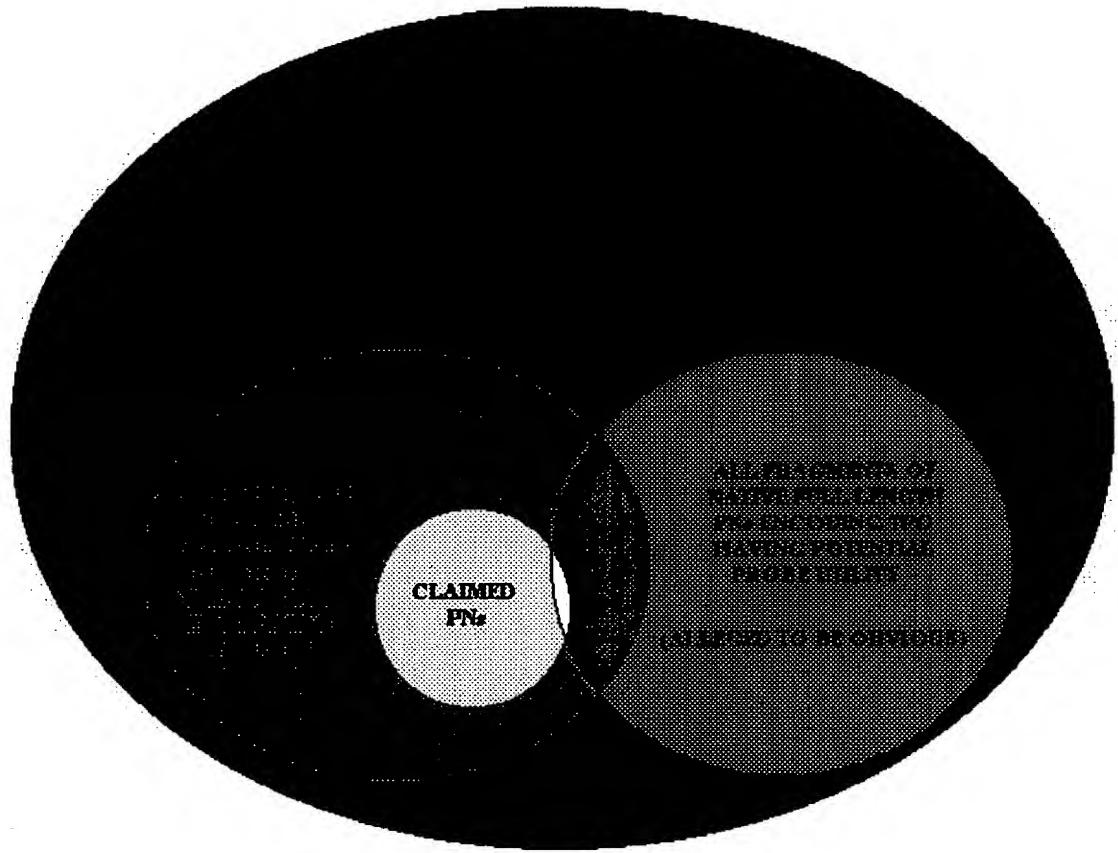
Retail drug store's sale, without authorization from plaintiff, of plaintiff's cosmetic products under plaintiff's mark does not give rise to cause of action for trademark infringement under Lanham Act, even though plaintiff alleges that its products are not "genuine" because they are sold in defendant's store without professional cosmetologist consultation that is supposed to be available when consumers purchase plaintiff's products, since plaintiff has failed to show any consumer confusion or deception, nor does drug store's sale of plaintiff's products violate Lanham Act's Section 43(a), 15 USC 1125(a), since that section does not provide cause of action merely for unauthorized stocking and sale of manufacturer's products, absent more culpable conduct by seller.

Appeal from the U.S. District Court for the Western District of Louisiana, Scott, J.

Action by Matrix Essentials Inc. against Emporium Drug Mart Inc. of Lafayette, d/b/a Drug Emporium, for trademark infringement and unfair competition, in which Emporium filed counterclaim alleging antitrust violations. From federal district court's decision granting summary judgment dismissing both plaintiff's claims and counterclaim, parties cross-appeal. Affirmed.

Louis A. Colombo, of Baker & Hostetler, Cleveland, Ohio; Theresa M. Gallion, of Baker & Hostetler, Orlando, Fla.; and Louis Simon, II, of Laborde & Neuner, Lafayette, La., for plaintiff.

APPENDIX G



IN RE BELL SPECIFICALLY APPLIES TO OVERLAPPED CLAIMED PN's (WHITE SECTION)

BEST AVAILABLE COPY